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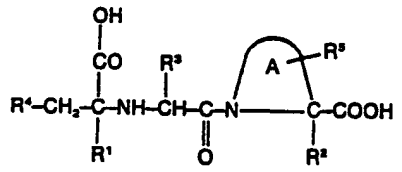
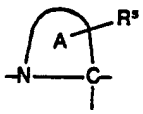
(54) Carboxyalkyl dipeptides, processes for their production and pharmaceutical compositions containing them.

(57) The compounds of the present invention are compounds of the formula



I

and the pharmaceutically acceptable esters and salts thereof wherein R^1 and R^2 independently are hydrogen or lower alkyl;
the group



is one of the structures II to VIII specified in the description, one of R^3, R^4 and R^5 is a group $Z-(CH_2)_{0-4}-$, wherein Z is selected from Z^1 to Z^{10} being as defined in the description and the other of the groups R^3, R^4 and R^5 are as also defined. The compounds are useful as antihypertensive agents, in the treatment of congestive heart failure and glaucoma. Their preparation and pharmaceutical compositions are disclosed.

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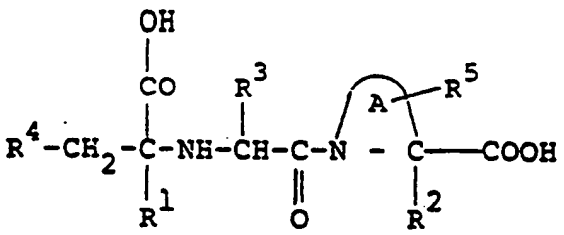
Carboxyalkyl dipeptides, processes for their production and pharmaceutical compositions containing them.

The present invention relates to carboxyalkyl dipeptides substituted with groups containing one sulfamoyl group. The compounds are useful as antihypertensive agents, in the treatment ofcongestive heart failure and glaucoma.

Carboxyalkyl dipeptides which are useful as inhibitors of angiotensinconverting enzyme and as antihypertensive agents are known from the published European patent applications Nos. 12401 and 50800.

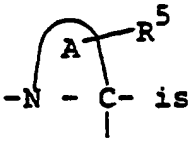
The compounds of the present invention are compounds of the formula

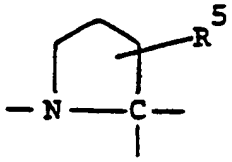


I

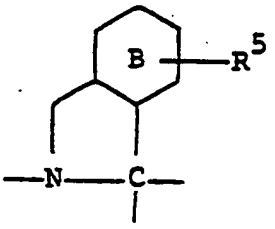
and th pharmaceutically acceptable esters ther of and the pharmaceutically acceptable salts of the free compounds and the esters, wherein

R^1 and R^2 independently are hydrogen or lower alkyl;

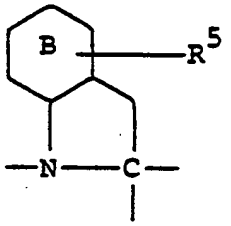
the group  is one of the structures II to VIII



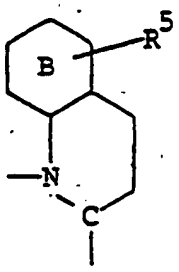
II



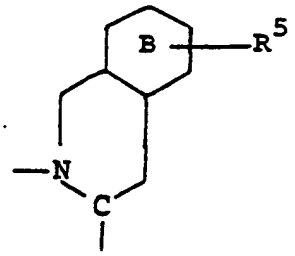
III



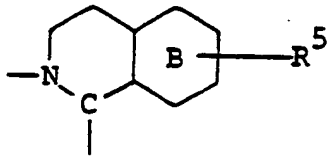
IV



V

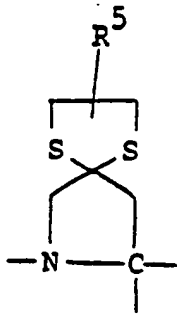


VI



VII

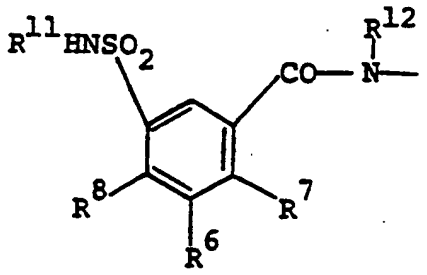
(wherein B is a saturated or aromatic ring) or



VIII

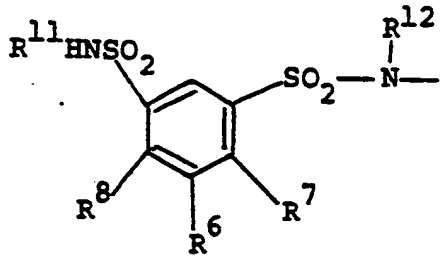
one of R^3, R^4 and R^5 is a group $Z-(CH_2)_{0-6}-$, wherein Z has one of the following values Z^1 to Z^{10}

Z^1:



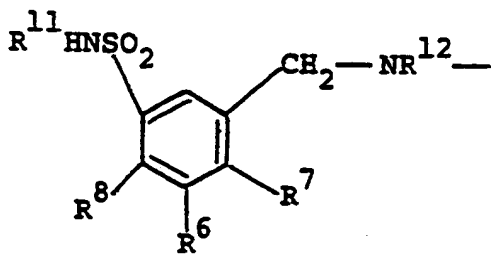
IX

Z^2:



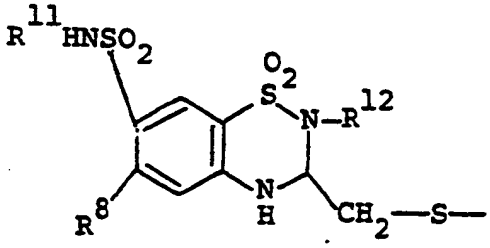
X

Z^3:



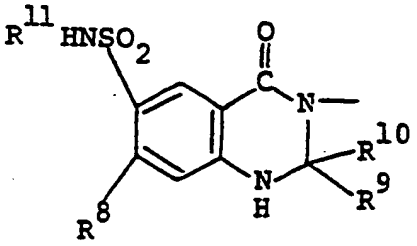
XI

Z^4:



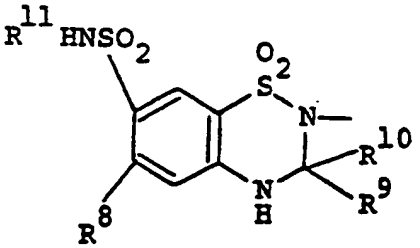
XII

Z^5:



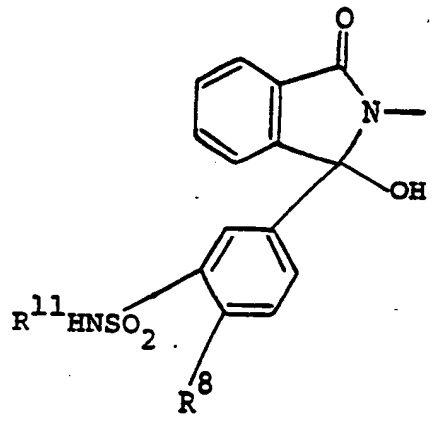
XIII

Z^6:



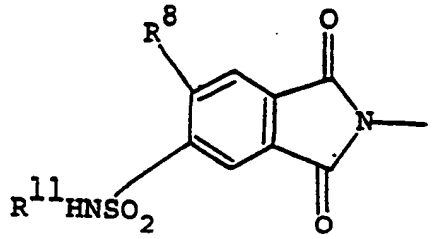
XIV

Z^7:



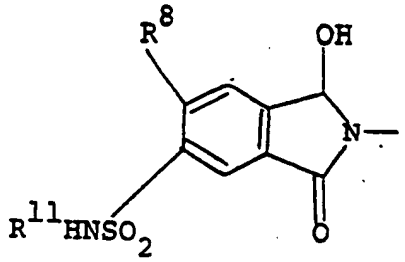
XV

Z^8:



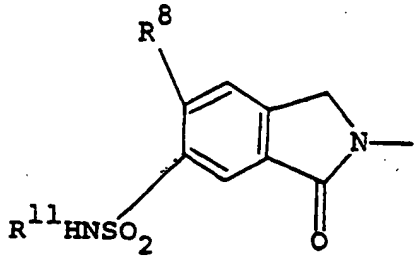
XVI

Z^9:



XVII

Z^{10}:



XVIII

wher in R^8 is Cl or CF_3;

R^6 is hydrogen or halogen;

R^7 is hydrogen, halogen, carboxy, hydroxy or amino;

R^9 and R^{10} are independently hydrogen, lower alkyl or halo-lower alkyl and R^9 can also be phenyl or phenyl lower alkyl;

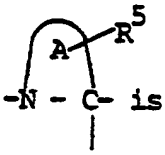
R^{11} is hydrogen or lower alkyl;

R^{12} is hydrogen, lower alkyl or phenyl lower alkyl;

whereby when R^3 is the group $Z-(CH_2)_{0-6}-$, then

R^3 is $Z^1-(CH_2)_{1-6}-$, $Z^2-(CH_2)_{1-6}-$, $Z^3-(CH_2)_{1-6}-$, Z^4-CH_2-, $Z^5-(CH_2)_{1-6}-$, $Z^6-(CH_2)_{1-6}-$, $Z^7-(CH_2)_{1-6}-$, $Z^8-(CH_2)_{1-6}-$, $Z^9-(CH_2)_{1-6}-$, or $Z^{10}-(CH_2)_{1-6}-$,

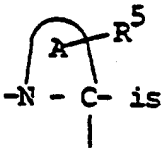
R^4 is lower alkyl, benzyl, benzyloxy, benzylthio, phenoxy, or phenylthio,

R^5 is hydrogen; and the group  is one of the structures II to VIII;

and when R^4 is the group $Z-(CH_2)_{0-6}-$, then

R^4 is $Z^1-(CH_2)_{0-6}-$, $Z^2-(CH_2)_{0-6}-$, $Z^3-(CH_2)_{0-6}-$, $Z^4-(CH_2)_{0-6}-$, $Z^5-(CH_2)_{0-6}-$, $Z^6-(CH_2)_{0-6}-$, $Z^7-(CH_2)_{0-6}-$, $Z^8-(CH_2)_{0-6}-$, $Z^9-(CH_2)_{0-6}-$ or $Z^{10}-(CH_2)_{0-6}-$ and

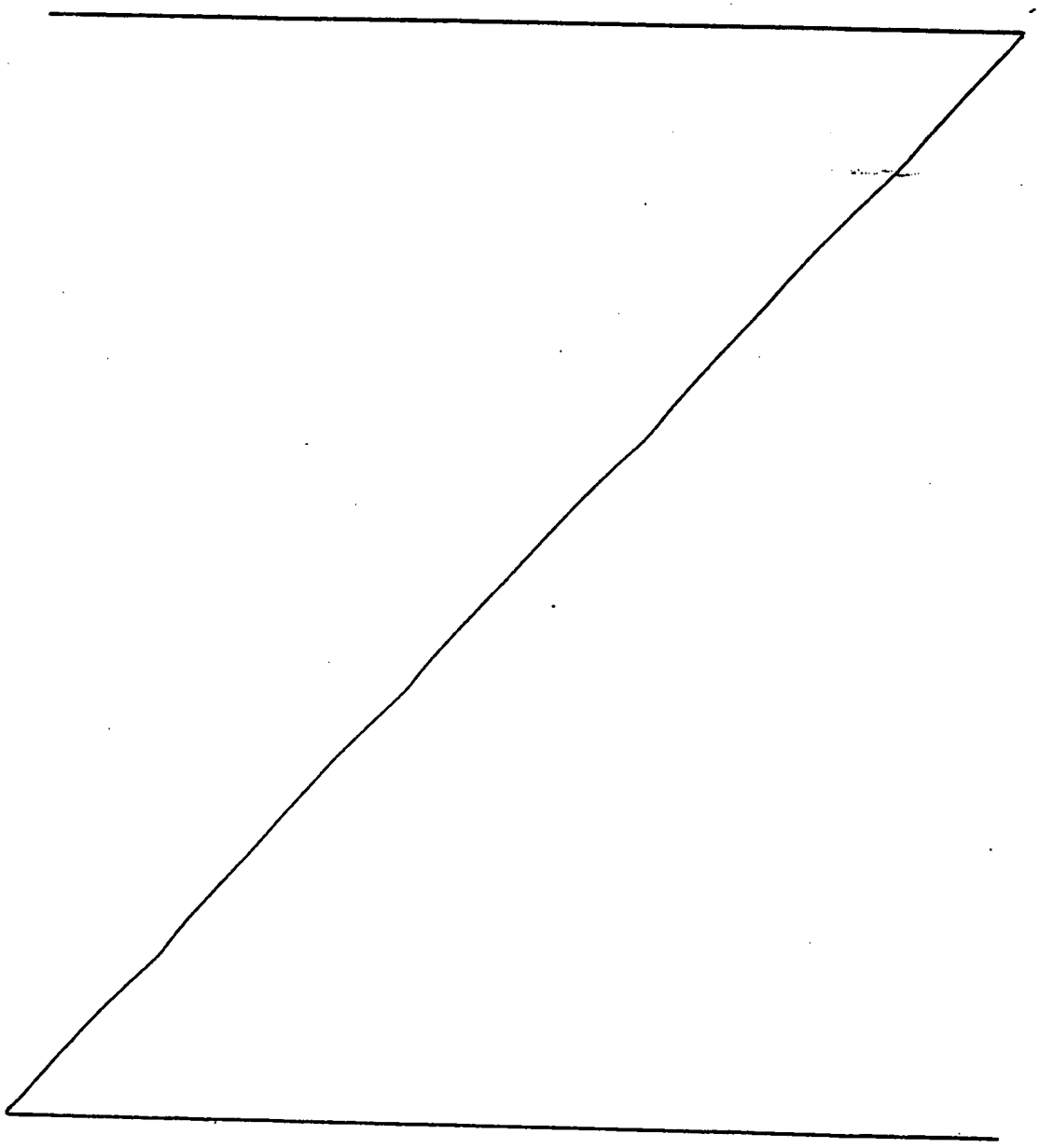
R^3 is hydrogen, lower alkyl or amino lower alkyl and

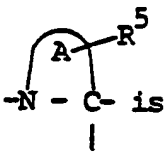
R^5 is hydrogen; and the group  is one of the structures II to VIII;

and when R^5 is the group $Z-(CH_2)_{0-6}-$, then R^5 is Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, Z^9 or Z^{10},

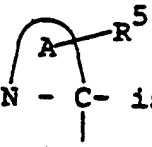
R^3 is hydrogen, lower alkyl or amino lower alkyl and

R^4 is lower alkyl, benzyl, benzyloxy, benzylthio, phenoxy or phenyl-



thio; and  the group -N - C- is one of the structures II to VII.

One embodiment of the present invention comprises compounds of formula I, its esters and salts, wherein R^4 is the group $Z-(CH_2)_{0-6}-$. Among these compounds certain groups of compounds are preferred:

.) compounds, wherein the group  -N - C- is the group of formula II, IV (wherein B is a saturated ring) or VIII, preferably R^5 being hydrogen;

.) compounds, wherein R^4 is $Z-(CH_2)_{0-6}-$, Z being Z^1, Z^2, Z^3, Z^5, Z^7, Z^8, Z^9 or Z^{10};

.) compounds, wherein R^4 is $Z^1-(CH_2)_{2 \text{ or } 3}-$, $Z^2-(CH_2)_{2 \text{ or } 3}-$, $Z^3-(CH_2)_{2 \text{ or } 3}-$, $Z^5-(CH_2)_{2 \text{ or } 3}-$, $Z^7-(CH_2)_{2 \text{ or } 3}-$, $Z^8-(CH_2)_{2 \text{ or } 3}-$, $Z^9-(CH_2)_{2 \text{ or } 3}-$ or $Z^{10}-(CH_2)_{2 \text{ or } 3}-$;

.) compounds, wherein R^4 is Z^4;

.) compounds, wherein R^1 and R^2 are hydrogen;

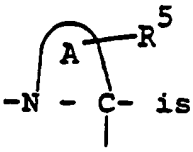
.) compounds, wherein R^6 is hydrogen and R^7 is hydrogen or hydroxy;

.) compounds, wherein R^9 and R^{10} are independently hydrogen or methyl;

.) compounds, wherein R^8 is chloro;

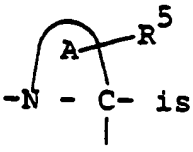
.) compounds, wherein R^3 is methyl;

.) compounds, wherein R^1 and R^2 are ind pendently hydrogen or lower alkyl (preferably hydrogen), th group

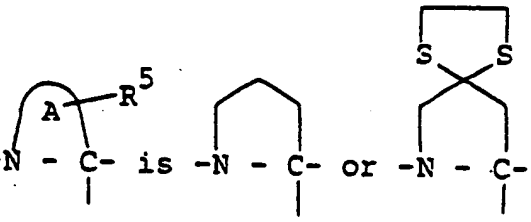


is th group of formula II r IV, wherein B is a saturated ring and R^5 is hydrogen, R^4 is Z^1-$(CH_2)_3$-, Z^2-$(CH_2)_3$- or Z^4, R^6 and R^7 are hydrogen and R^8 is chloro; and R^3 is hydrogen, lower alkyl or amino lower alkyl (preferably methyl);

.) of particular interest are compounds, wherein R^1 and R^2 are hydrogen, the group



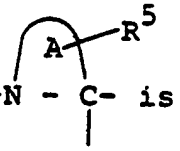
is the group of formula IV wherein B is a saturated ring, and R^5 is hydrogen, R^4 is Z^1-$(CH_2)_3$- or Z^2-$(CH_2)_3$-, wherein R^6 is hydrogen, R^7 is hydrogen or hydroxy, and R^8 is chloro, and R^3 is methyl, preferably in the form of its mono-or-di-ethyl ester. Also the analogous compounds, wherein the group



are preferred.

Another embodiment of the present invention comprises compounds of formula I, its esters and salts, wherein R^3 is the group Z-$(CH_2)_{0-6}$-. Among these compounds the following groups of compounds are preferred:

.) compounds, wherein the group



is the group of formula II, IV (wherein B is a saturated ring) or VIII;

.) compounds, wherein R^3 is Z^1-$(CH_2)_4$-, Z^2-$(CH_2)_4$-, Z^3-$(CH_2)_4$-, Z^4-CH_2-, Z^5-$(CH_2)_4$-, Z^6-$(CH_2)_4$-, Z^7-$(CH_2)_4$-, Z^8-$(CH_2)_4$-, Z^9-$(CH_2)_4$- or Z^{10}-$(CH_2)_4$-;

.) compounds, wherein R^1 and R^2 are hydrogen;

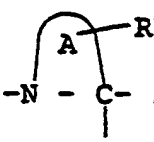
.) compounds, wherein R^6 is hydrogen and R^7 is hydrogen or hydroxy;

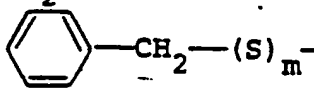
.) compounds, wherein R^9 and R^{10} are independently hydrogen or methyl;

.) compounds, wherein R^8 is chloro;

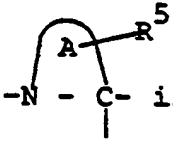
.) compounds, wherein R^4 is benzyl or ethyl;

.) compounds, wherein R^1 and R^2 are independently hydrogen or lower alkyl (preferably hydrogen), the group

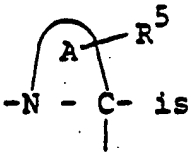
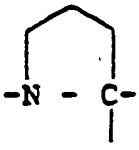
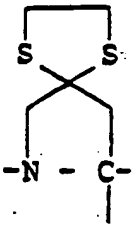


-N - C- is the group of formula II or IV, wherein B is a saturated ring, and R^5 is hydrogen, R^3 is Z^1-$(CH_2)_4$-, Z^2-$(CH_2)_4$- or Z^4-CH_2-, R^6 and R^7 are hydrogen and R^8 is chloro and R^4 is  wherein m is zero or 1,

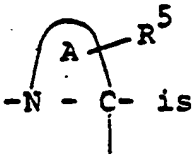
.) of particular interest are compounds, wherein R^1 and R^2 are hydrogen, the group

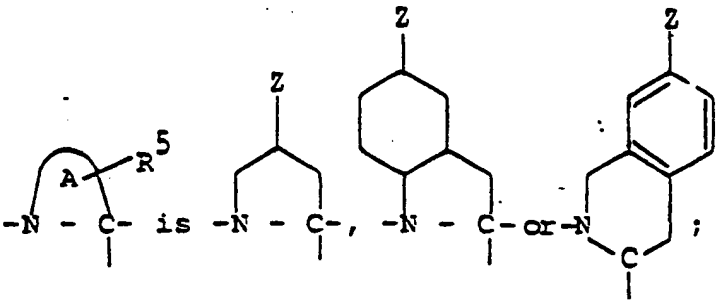


-N - C- is the group of formula IV, wherein B is a saturated ring and R^5 is hydrogen, R^3 is Z^1-$(CH_2)_4$- or Z^2-$(CH_2)_4$-, wherein R^6 and R^7 are hydrogen, R^8 is chloro; and R^4 is benzyl, preferably in the form of its mono-or-di-ethyl ster. Als the analogous compounds, wherein

the group  is  or  are preferred.

Another embodiment of the present invention comprises compounds of formula I, its esters and salts, wherein R^5 is the group $Z-(CH_2)_{0-6}-$. Among these compounds the following groups of compounds are preferred:

.) compounds, wherein the group  is the group of II, VI (wherein B is an aromatic ring), or IV (wherein B is a saturated ring);

.) compounds, wherein the group  ;

.) compounds, wherein R^5 is Z^1, Z^2, Z^3, Z^5, Z^7, Z^8, Z^9 or Z^{10};

.) compounds, wherein R^1 and R^2 are hydrogen;

.) compounds, wher in R^6 is hydrogen and R^7 is hydrogen or hydroxy;

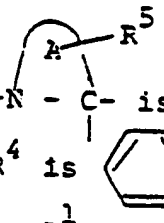
.) compounds, wherein R^9 and R^{10} are independently hydrogen or methyl;

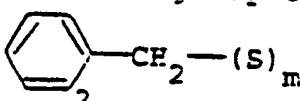
.) compounds, wherein R^8 is chloro;

.) compounds, wherein R^3 is methyl;

.) compounds, wherein R^4 is benzyl or ethyl;

.) compounds, wherein R^1 and R^2 are independently hydrogen or lower alkyl, the group



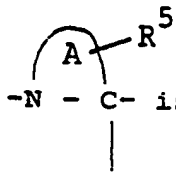
$-N-C-$ is the group of formula III, IV, V, VI or VII, R^4 is  , wherein m is zero or 1 and R^5 is Z^1 or Z^2, wherein R^6 and R^7 are hydrogen and R^8 is chloro, and R^3 is hydrogen or lower alkyl (preferably methyl).

The lower alkyl groups, except where noted otherwise, include straight and branched chain hydrocarbon radicals from one to six carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, cyclopropyl, cyclohexyl and the like.

The compounds of this invention form esters. In these esters the hydroxy group of the carboxy groups shown in formula I can be replaced by the same or by different groups which are selected from alkoxy having from 1 to 8

carbon atoms, phenoxy, phenylalkyloxy having from 7 to 10 carbon atoms, $-OCH_2OCO$-alkyl having from 3 to 8 carbon atoms, $-OCH_2CO$-phenyl, $-O(CH_2)_k$-O- phenyl wherein k is 1 or 2 and the phenyl ring may be substituted by halogen, hydroxy, trifluoromethyl, alkoxy having from 1 to 6 carbon atoms, alkyl having from 1 to 6 carbon atoms (the phenyl group preferably containing one substituent) and $-O(CH_2)_k$-O-napthyl wherein k is 1 or 2.

Preferred are alkyl esters (the alkyl group being defined as above) and aryl esters, especially the ethyl and benzyl esters. Of particular interest are the mono-esters, wherein the carboxy group attached to the group



is in the free form.

The compounds of this invention form salts with various inorganic and organic acids and bases which are also within the scope of the invention. Such salts include ammonium salts, alkali metal salts like sodium and potassium salts (which are preferred), alkaline earth metal salts like the calcium and magnesium salts, salts with organic bases e.g., dicyclohexylamine salts, N-methyl-D-glucamin , salts with amino acids like arginine, lysine

and the like. Also, salts with organic and inorganic acids may be prepared, e.g., HCl, HBr, H_2SO_4, H_3PO_4, methanesulfonic acid, toluensulfonic acid, maleic acid, fumaric acid and camphorsulfonic acid. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, e.g., in isolating of purifying the product.

This invention includes all possible stereoisomers of the compounds. Preferred stereoisomers are those in which the absolute configurations at each of the three carbon atoms bonded to both a nitrogen and a carbonyl group corresponds most closely to the absolute configuration of L-aminoacids. The preferred compounds contain a cis, syn-octahydro-1H-indole-2(S)-carboxylic acid moiety or a 1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid moiety.

Non limiting examples of preferred compounds of the present invention are:

1-{N-[1(S)-ethoxycarbonyl-5-(4-chloro-3-sulfamoyl)-benzenesulfonaminopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid,

1-{N-[1(S)-ethoxycarbonyl-5-(4-chloro-3-sulfamoyl)-benzamidopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indol -2(S)-carboxylic acid,

1-{N-[1(S)-ethoxycarbonyl-5-(4-chloro-2-hydroxy-5-sulfamoyl)-benzamidopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid,

1-{Nα-[1(S)-ethoxycarbonyl-3-phenylpropyl]-Nε-[(4-chloro-3-sulfamoyl)benzenesulfonyl]-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid,

1-{Nα-[1(S)-ethoxycarbonyl-3-phenylpropyl]-Nε-[(4-chloro-3-sulfamoy)benzoyl]-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid,

7-(4-chloro-3-sulfamoylbenzamido)-2-{N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl}-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid,

1-{N-[1 (S)-CARBOXY-5-[[(4-CHLORO-2-HYDROXY-5-SULFAMOYL PHENYL) CARBONYL]AMINO]PENTYL]-(S)-ALANYL}-CIS,SYN-OCTAHYDRO-1H-INDOLE-2(S)-CARBOXYLIC ACID,

1-{N-[1(S)-CARBOXY-5-[[(4-CHLORO-3-(N-METHYL SULFAMOYL) PHENYL] CARBONYL]AMINO]PENTYL]-(S)-ALANYL}-CIS,SYN-OCTAHYDRO-1H-INDOLE-2(S)-CARBOXYLIC ACID,

1-{N-[1(S)-CARBOXY-5-[[(4-CHLORO-3-SULFAMOYL PHENYL) CARBONYL]AMINO]PENTYL]-(S)-ALANYL}-CIS,SYN-OCTAHYDRO-1H-INDOLE-2(S)-CARBOXYLIC ACID,

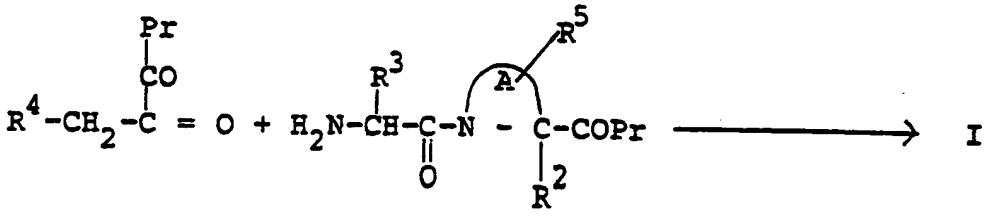
1-[N-[1(S)-ETHOXYCARBONYL-5[[(4-CHLORO-2-AMINO-5-SULFAMYLPHENYL)-CARBONYL]AMINO]PENTYL]-(S)ALANYL]-CIS,SYN-OCTAHYDRO-1H-INDOLE-2(S)CARBOXYLIC ACID

1-{N-[1(S)-ethoxycarbonyl-5-[7-chloro-4-oxo-6-sulfamyl-2-phenyl-1,2,3,4-tetrahydro quinazolin-3-yl]pentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S) carboxylic acid

or the corresponding free ~~fiii~~ acids or esters, respectively.

The compounds of the present invention can be produced by one or more of the methods and subroutes depicted in the following equations. Reactive groups not involved in the reactions described below such as amino and carboxy groups may be protected by methods standard in peptide chemistry prior to the coupling reactions and subsequently deprotected to obtain the desired products. Racemates, if obtained by these processes, can be resolved by standard techniques such as column chromatography or fractional crystallization.

A. For the preparation of compounds of formula I, wherein R^1 is hydrogen a ketocompound (XIX) is condensed with a dipeptide (XX) under reduction.

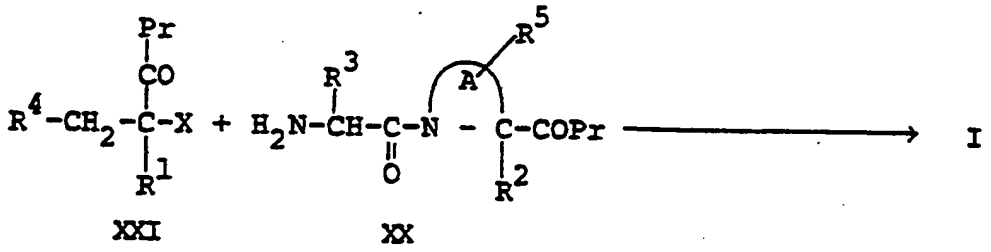


XIX XX

In these compounds A, R^2, R^3, R^4 and R^5 are as defined above and Pr stands for a free or a protected (e.g. by esterification) hydroxy group.

The ketocompound (XIX) can be condensed with the dipeptide (XX) in aqueous solution, optimally near neutrality, or in a suitable organic solvent (for example CH_3OH) in the presence of a reducing agent such as for example sodium cyanoborohydride to give directly the desired compound I (wherein R^1 is hydrogen). Alternatively, the intermediat Schiff base, enamine, or aminol may be catalytically reduced to yield product I, for example, by hydrogen in the presence of palladium on carbon (e.g. 10% palladium on carbon) or of Raney nickel. The ratio of diasteriomeric products formed may be altered by the choice of catalyst.

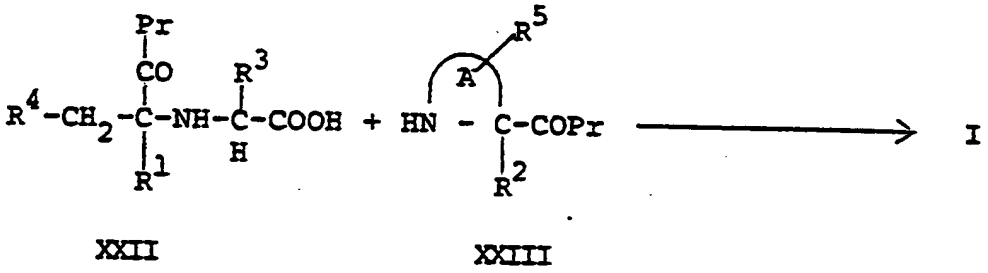
B. Alkylation of a dipeptide (XX) by means of a compound of formula (XXI)



XXI XX I

wherein X is chloro, bromo, iodo, alkanesulfonyloxy or arenesulfonyloxy, R^1, R^2, R^3, R^4, R^5 are as defined above for compounds of formula I and Pr stands for a free or protected (e.g. by esterification) hydroxy group. The reaction can be carried out under basic conditions in water or in an organic solvent.

C. Condensation of an aminoacid (XXII) with an aminoacid (XXIII)



XXII XXIII I

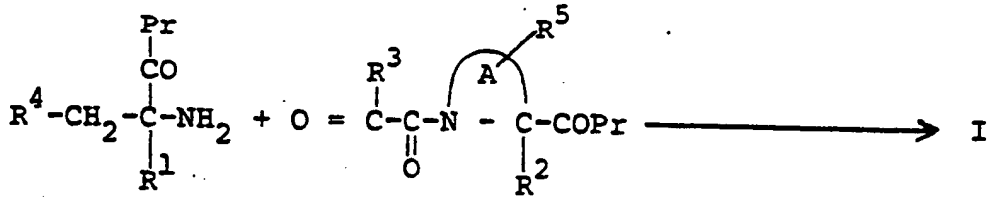
A, R^1, R^2, R^3, R^4, R^5 are as defined above for compounds formula I and Pr stands for a free or protected (e.g. esterification) hydroxy group.

This reaction is well known from peptide chemistry. The reaction can be carried out in the presence of a condensing agent such as for example dicyclohexylcarbodiimide (DCC), diphenylphosphoryl azide (DPPA) and N,N-disuccinimidyl carbonate in CH_3CN. While, as mentioned above, reactive groups (e.g. hydroxy groups) are protected before the coupling reaction is carri d out, the amino group of compound (XXIII)

can b activated, .g. by means of tetraethyldiphosphit and/or the carboxy group of compound (XXII) can be activated via the intermediacy of active esters such as that derived from 1-hydroxybenzotriazole, its mixed anhydride (derived from a chlorocarbonic acid ester), its azide or dicyclohexylcarbodiimide.

This process is of particular use for the preparation of compounds wherein the R^3, R^4 or R^5 contains or is Z^1, especially wherein R^4 is or contains Z^1.

D. Condensation of an amino compound (XXIV) with a keto-compound (XXV)

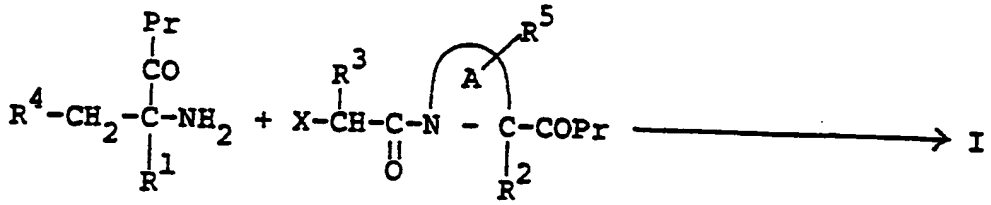


XXIV XXV I

under the conditions described for process A.

A; R^1, R^2, R^3, R^4, R^5 are as defined above for compounds formula I and Pr stands for a free or protected (e.g. by esterification) hydroxy group.

E. Alkylation of an amino compound (XXIV) by means of a compound (XXVI)

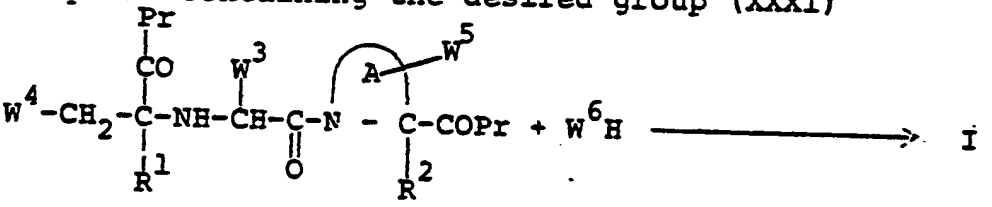


XXIV XXVI

wherein X is chloro, bromo, iodo, alkanesulfonyloxy or arenesulfonyloxy, A, R^1, R^2, R^3, R^4, R^5 are as defined above for compounds of formula I, and Pr stands for a free or protected (e.g. by esterification) hydroxy group. The reaction can be carried out under the conditions described for process B.

F. For the preparation of compounds of formula I, wherein one of R^3, R^4 and R^5 is a group $Z-(CH_2)_{0-6}-$, wherein Z is Z^5, Z^6, Z^7, Z^8, Z^9 or Z^{10} preferably Z^7, Z^8 or Z^9:

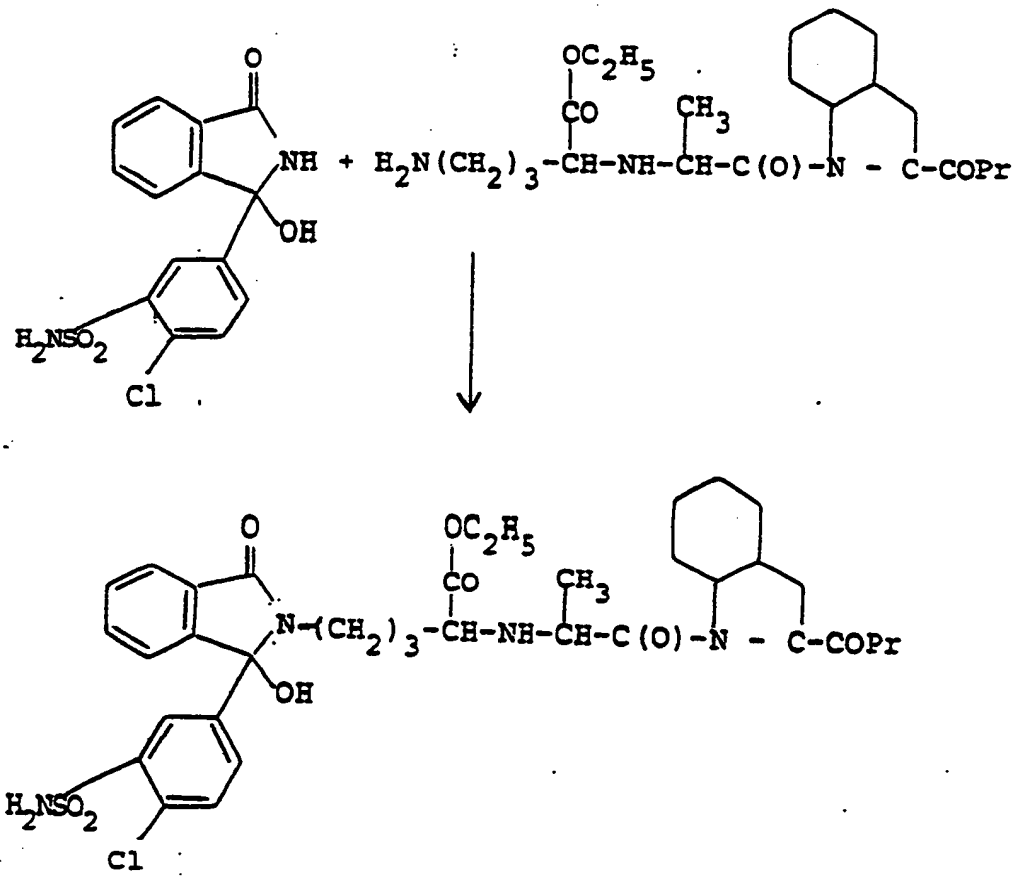
Condensation of a peptide of the general formula (XXX) with a compound containing the desired group (XXXI)



XXX XXXI

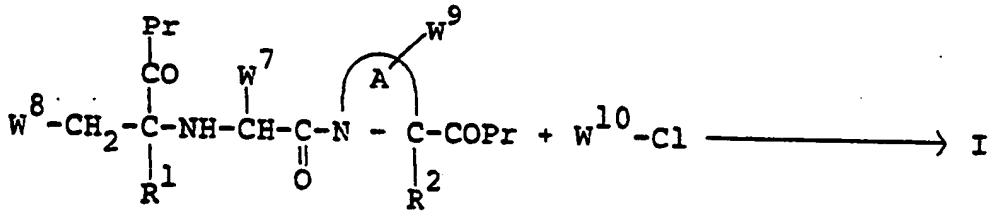
wherein R^1, R^2 and A are as defined for formula I, Pr is a protected hydroxy group, W^3, W^4 and W^5 are defined like R^3, R^4 and R^5 respectively with the difference that one of W^3, W^4 and W^5 contains an NH_2-group instead of the respctive Z^5 to Z^{10}-group; and W^6 is Z^5, Z^6, Z^7, Z^8, Z^9 or Z^{10}. The reaction can be carried out in an inert organic solvent, e.g. an alcohol, (preferably ethanol) at reflux temperature.

This reaction may be exemplified by the following Reaction Scheme:



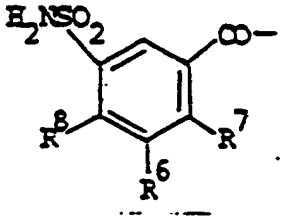
G. For the preparation of compounds of formula I, wherein one of R^3, R^4 and R^5 is a group $Z-(CH_2)_{0-6}-$, wherein Z is z^1, z^2 or z^3:

condensation of a peptide of formula XXXII with an appropriately substituted compound of formula XXXIII

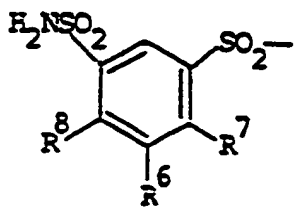


XXXII XXXIII

wherein R^1, R^2 and A ar as defined for formula I, Pr is a protected hydroxy group, W^7, W^8 and W^9 are defined like R^3, R^4 and R^5 respectively, with the difference that one of W^7, W^8 and W^9 contains an NH_2-group instead of the respective Z^1, Z^2 or Z^3 group, and W^{10} is

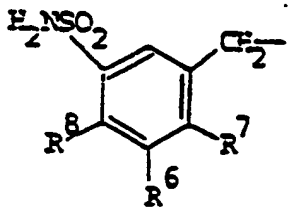


XXXIV



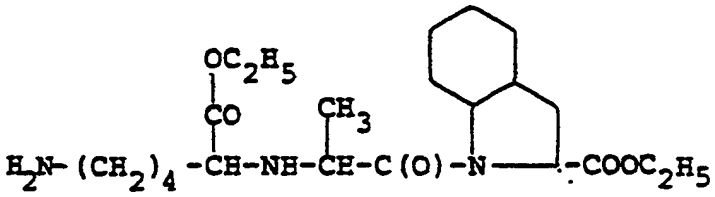
XXXV

or



XXXVI

This condensation can be exemplified by the following Reaction Scheme:



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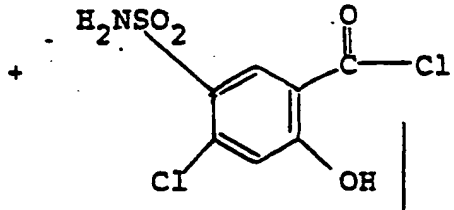
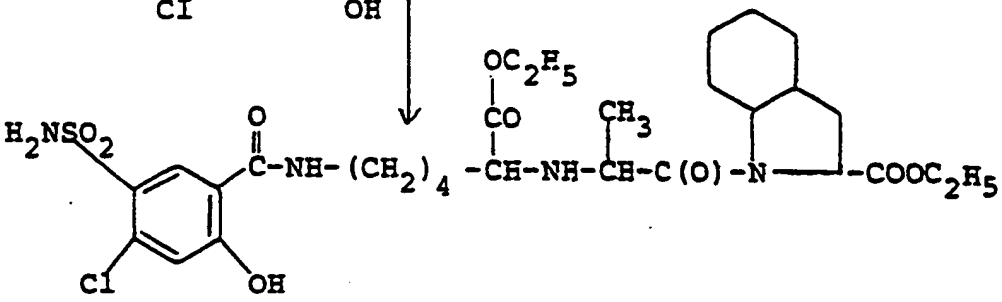
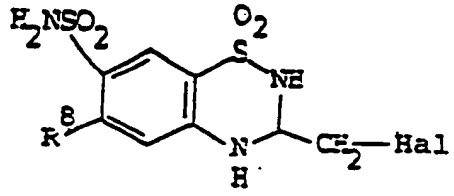




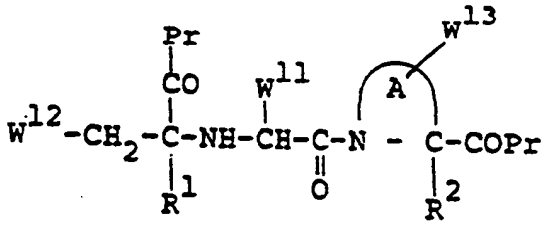
The reaction can be carried out in a suitable solvent (e.g. THF, pyridine or mixture of THF and triethylamine), usually between 0°C and room temperature.

H. For the preparation of compounds of formula I, wherein one of R^3, R^4 and R^5 is a group $Z-(CH_2)_{0-6}-$, wherein Z is Z^4: condensation of a peptide of formula (XXXVII) with a 3-halomethylbenzothiadiazine (XXXVIII)



XXXVIII

+ ⟶ I

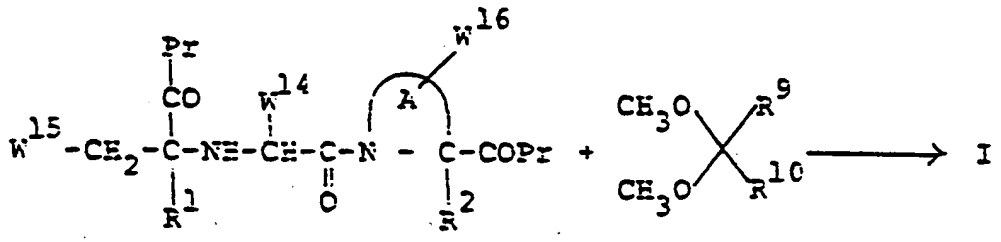


XXXVII

wherein R^1, R^2 and A are as defined for formula I, Pr is a protected hydroxy group, W^{11}, W^{12} and W^{13} ar defined like R^3, R^4 and R^5 respectively with the diff rence that one of W^{11}, W^{12} and W^{13} contains a -SH-group instead of the respective Z^4-group, and Hal is halogen, preferably chloro.

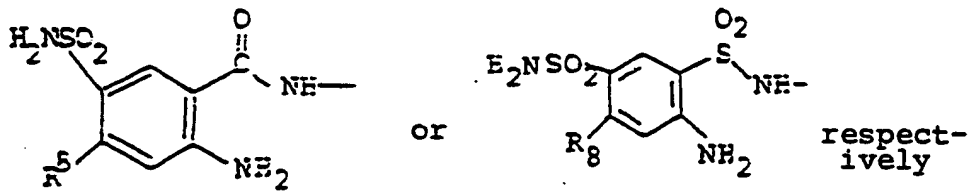
The reaction is carried out in a suitable solvent (e.g. DMF), preferably in the presence of triethylamine.

I. For the preparation of compounds of formula I, wherein one of R^3, R^4 and R^5 is a group $Z-(CH_2)_{0-6}-$, wherein Z is Z^5 or Z^6: condensation of a peptide of formula XXXIX with a compound of formula XXXX



XXXIX XXXX

wherein R^1, R^2, R^9, R^{10} and A are as defined for formula I, Pr is a protected hydroxy group, W^{14}, W^{15} and W^{16} are defined like R^3, R^4 and R^5 respectively with the difference that one of W^{14}, W^{15} and W^{16} contains the group

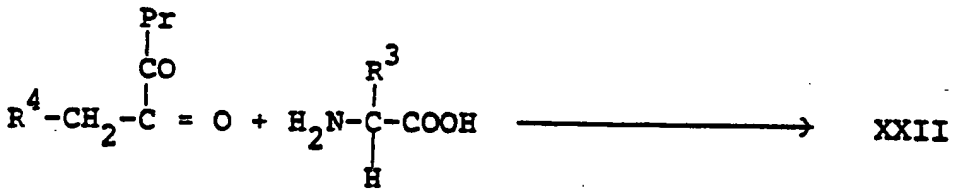


XXXXI XXXXI a

instead of the group Z^5 or Z^6 resp ctively. The reaction can be carried out in an inert organic solvent, e.g. an alcohol, preferably ethanol, under acidic conditions (e.g. by addition of a hydrochloric acid) at reflux temperature.

The starting compounds in these reactions can be prepared according to known methods.

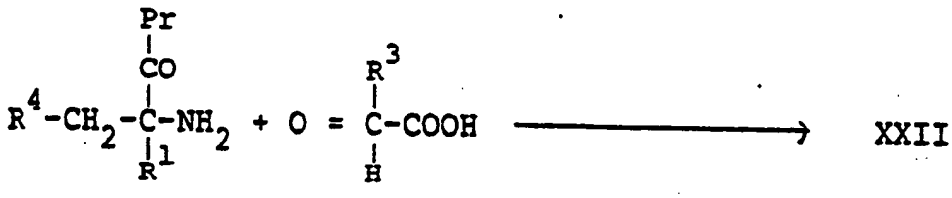
The compound of formula XXII, wherein R^1 is hydrogen can for example be prepared by reacting a keto compound (XIX) with on aminoacid (XXVII)



XIX XXVII XXII

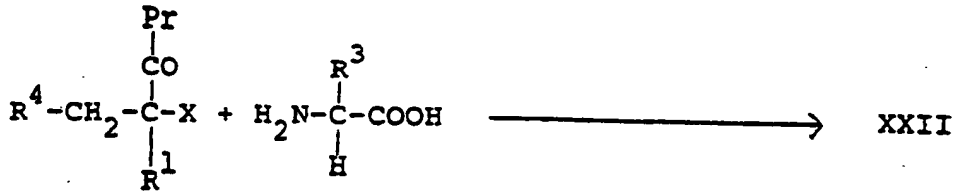
according to the condition described in process A.

Alternatively, the compound of formula XXII can be prepared by condensing XXIV with a keto acid (XXVIII)

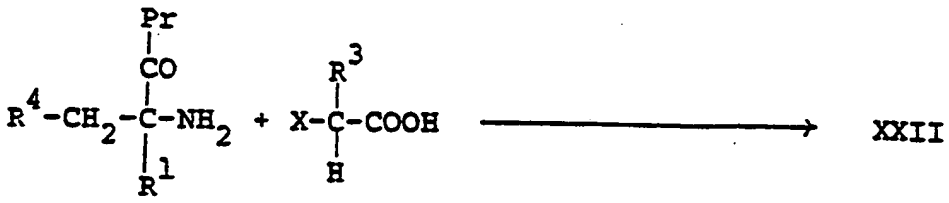


XXIV XXVIII XXII

or by condensing



XXI XXVII XXII



XXIV XXIX XXII

under the conditions described for process B (X being as defined in process B).

The compound XXII can also be prepared analogously to process G described above.

The starting compound (XXXVII) of process H can for example be prepared from a correspondign compound wherein the respective group W^{11}, W^{12} or W^{13} is $-SCHC_6H_5$ by reduction with sodium in liquid ammonia.

The above processes are followed by setting free protected groups by known methods. Protected carboxy groups, e.g. when, for example, protected by removable ester groups (e.g. Pr being alkoxy, (methoxy, ethoxy, tert. butyloxy), nitrobenzyloxy or bezyloxy,) are set free by hydrolysis or hydrogenation. (Reductive cleavage of a compound, wherein one of the protecting groups (Pr) is benzyloxy and th other protecting group is alkoxy will yield a compound, wherein the benzyloxy group has been replaced by hydr xy

but the alkoxy group has not been replaced.) Hydrolysis can be carried out under acidic conditions (using .g. a halogen hydracid or trifluoroacetic acid), under basic conditions or by means of photochemical hydrolysis.

The amino group(s) can be protected by protecting groups such as for example formyl, t-butoxycarbonyl, carbobenzyloxy, triphenylmethyl and nitrophenylsulfenyl. These groups can be removed under acidic conditions, e.g. by means of a halogenhydroacid and/or trifluoroacetic acid.

Esters obtained by the above processes can also be transesterified. For example, ethyl esters can be converted to the corresponding benzyl ester with benzyl alcohol under acidic conditions.

As mentioned before the compounds of this invention exist in diastereoisomeric forms or in mixtures thereof. The above described syntheses can utilize racemates, enantiomers or diastereomers as starting materials. Enantiomeric intermediates may be obtained by resolution methods known in the art. When diastereomeric products result from the synthetic procedures, the diastereomeric products can be separated by conventional chromatographic or franctional crystallization m thods (e.g. describ d in the Europ an published application No. 12401).

The compounds of this invention form salts with various inorganic and organic acids and bases which are also within the scope of the invention. Such salts include ammonium salts, alkali metal salts like sodium and potassium salts (which are preferred), alkaline earth metal salts like the calcium and magnesium salts, salts with organic bases e.g., dicyclohexylamine salts, N-methyl-D-glucamine, salts with amino acids like arginine, lysin and the like. Also, salts with organic and inorganic acids may be prepared, e.g., HCl, HBr, H_2SO_4, H_3PO_4, methanesulfonic acid, toluensulfonic acid, maleic acid, fumaric acid and camphorsulfonic acid. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, e.g., in isolating or purifying the product.

The salts may be formed by conventional means, as by reacting the free acid or free base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the cations of an existing salt for another cation on a suitable ion exchange resin.

The compounds of this invention are useful as antihypertensiv agents in mammals, including humans, in which th

blood pressure has become abnormally elevated.

The compounds of the present invention can be combined with pharmaceutical carriers and administered in a variety of well known pharmaceutical forms suitable for oral or parenteral administration to provide compositions useful in the treatment of cardiovascular disorders and particularly mammalian hypertension.

The effective dose (ED_{50}) of the compounds of this invention will typically be in the range of about 0.01 to about 30mg/kg, preferable of about 0.1 to about 10mg/kg, of mammalian weight, administered in single or divided doses. The exact dose to be administered is dependent upon where the particular compound lies within the above quoted range, as well as upon the age, weight and condition of the individual.

Generally, in treating humans, the compounds of this invention may be administered to patients in need of such treatment in a dosage range of 5 to 500mg per patient generally given several times, thus giving a total daily dose of from 5 to 2000mg per day.

The composition containing the compounds of this inv ntion will preferably contain from about 5 to 250mg of the active compound per dosage unit. These compositions are most preferably administered orally. Typical formulations for oral administration are those such as tablets, capsules, syrups, elixirs or suspensions. Typical injectable formulations include solutions and suspentsions.

The typical acceptable pharmaceutical carriers for use in the formulations described above are exemplified by: sugars such as lactose, sucrose, mannitol and sorbitol; starches such as corn starch, tapioca starch and potato starch; cellulose and derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate, polyvinylpyrrolidone, polyvinyl alcohol; stearic acid; alkalin earth metal stearates such as magnesium stearate and calcium stearate, stearic acid, vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene glycol polymers; beta-cyclodextrin; fatty alcohols and hydrolyzed cereal solids; as well as other non-toxic compatibl fill rs, binders, disintegrants, buff rs, pr s rvatives, antioxidants, lubricants, flavoring agents, and th like

commonly used in pharmaceutical formlations.

The following examples illustrate the preparation of the compounds of the present invention. The diasteromers prepared as setforth below may be isolated by column chromatography or by fractional crystallization.

In the examples below, octahydroindole-2(S)-carboxylic acid refers to cis,syn-octahydroindole-2(S)-carboxylic acid, also named 3a(S), 7a(S)-octahydroindole-2(S)-carboxylic acid.

Exampl 1

1{Nα-[1(S)-Ethoxycarbonyl-3-phenylpropyl]-Nℓ-[(4-chloro-3-sulfamoyl)benzenesulfonyl]-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid

A. Stir a suspension of 24.0g of Nℓ-benzyloxycarbonyl-(S)-lysine and 36.0g of ethyl 2-oxo-4-phenylbutanoate acid in 2500ml of absolute ethanol at room temperature for 24 hours. Add 16.0g of sodium cyanoborohydride and stir the resulting mixture at room temperature for 48 hours. Add 80ml of water and stir the resulting mixture at room temperature for 72 hours. Concentrate this mixture in vacuo at 30°C to give a white residue. Suspend the residue in 1200ml of ice water, add concentrated hydrochloric acid to maintain pH 2-4, and stir this mixture for 2 hours. Absorb this aqueous solution on 2000ml of XAD-2 (Rohm & Haas Co.) resin. Elute the r sin with 16,000ml of water and then with 8000ml of absolute ethanol. Concentrate the ethanol solution and chromatograph the residue on a column of silica gel (3000ml, 60-200 mesh) eluting with chloroform : isopropanol : 7% ammonium hydroxide 1:1:1 (organic layer) to give a white residue. Chromatograph this residue on a column of silica gel (3000ml), eluting with chloroform : isopropanol : 7% ammonium hydroxide 1:1:1 (organic layer) to give fractions A, B, C, and D. Absorb fraction B on a column of silica gel (1500ml), eluting with chloroform : isopropanol : 7% ammonium hydroxide 1:1:1 (organic layer) to give N -benzyloxycarbonyl-Nα-[1(S)-carboethoxy-3-(phenyl)propyl]-(S)-lysine, a white solid, $[\alpha]_D^{26}$+6.1° (ethanol), m.p. 114-115°C.

B. Cool a solution of 1.9g of the product of part A and 1.3g of cis,syn-octahydro-1H-indol -2(S)-carboxylic acid benzyl ster in 24ml of dimethylformamide t 0°C under nitrog n. Add dropwise a solution of 0.9 of diphenyl-

phosphorylazid in 6ml of dim thylformamide, follow d by a solution of 0.7ml of N-methylmorpholine in 6ml of dimethylformamide, also added dropwise, and stir at room temperature for 18 hours. Pour the reaction solution into wat r, adjust to pH 8 with 1N NaOH, and extract with ether. Dry the ether layer over magnesium sulfate, and concentrate under vacuum to a yellow oil. Chromatograph the oil on silica gel (1000ml, 60-200 mesh), eluting with hexane : ethyl acetate (1:2) to give 1-{Nα-[1(S)-carboethoxy-3-(phenyl)propyl]-Nε-benzyloxy-carbonyl-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid, benzyl ester, a yellow oil.

C. Dissolve 1.60g of the product of part B in 150ml of absolute ethanol. Add 0.75g of 10% palladium-on-charcoal and hydrogenate the mixture at 50 psi at room temperature. Filter the reaction mixture and concentrate the filtrate in vacuo to give 1-{Nα-[1(S)-ethoxycarbonyl-3-(phenyl)propyl-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid hydrate, a white foam, $[\alpha]_D^{26}$-42.5 (ethanol).

D. To 4.9g of 1-{Nα-[1(S)-[ethoxycarbonyl-3-phenylpropyl]-(S)-lysyl}-cis,syn-octahyro-1H-indole-2(S)-carboxylic acid in 200ml of tetrahydrofuran and 2g of triethylamine at 0-5°C, add 2.9g of 4-chloro-3-sulfamoylbenzenesulfonyl chloride and stir the resulting mixture at room temperature. Concentrate the resulting mixture in vacuo and chromatograph the residue on an Lobar RP-8, size B column (E. Merck) using acetonitrile : water as eluant to give the title compound.

Example 2

1-{Nα-[1(S)-Ethoxycarbonyl-3-phenylpropyl]-Nε-[(4-chloro-3-sulfamoyl)benzoyl]-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid

Treat 4.9g of 1-{Nα[1(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid (obtainable as described in Example 1A to 1C) in 200ml of tetrahydrofuran and 2.0g of triethylamine at 0-5°C with 2.2g of 4-chloro-3-sulfamoyl-benzoyl chloride and stir the resulting mixture at room temperature. Concentrate the resulting mixture in vacuo and chromatograph the residue on a Labor RP-8, size B column (E. Merck) using acetonitrile : water as eluant to give the title compound.

Example 3

1-{Nα-[1(S)-Ethoxycarbonyl-3-phenylpropyl]-Nε-[(4-chloro-3-sufamoyl)benzenesulfonyl]-(S)-lysyl}-(S)-proline

Substitute 2.17g of 1-{Nα-[1(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-lysyl}-(S)-proline for the respectively substituted octahydro-1H-indole-2(S)-carboxylic acid in Example 1D to obtain the title compound.

Example 4

1-{Nα-[1(S)-Ethoxycarbonyl-3-phenylpropyl]-Nε-[(4-chloro-3-sufamoyl) benzoyl] -(S)-lysyl}-(S)-proline

Substitute 2.17g of 1-{Nα-[1(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-lysyl}-(S)-proline for the r spectively substituted octahydro-1H-indole-2(S)-carboxylic acid in Ex-

ample 2 to obtain the title compound.

Example 5

1-{Nα-[1(S)-Carboxy-3-phenylpropyl]-Nε-[(4-chloro-3-sulfamoyl)benzenesulfonyl]-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid

A. To a solution of 1.10g of 1-{Nα[1(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-lysyl}-cis,syn-octahyro-1H-indole-2(S)-carboxylic acid (prepared as in Example 1) in 100ml of methanol at 0-5°C, add 2.0ml of 2.5N sodium hydroxide solution and stir at room temperature for 24 hours. Add 20ml of water, concentrate to one-half volume, and stir 24 hours. Concentrate this solution in vacuo and absorb on AG 50W-X2 (100-200 mesh, hydrogen form, Bio-Rad resin) (50ml). Place said 50ml of resin on an additional 300ml of resin, elute the resin with 1200ml of water, and then elute with 4% pyridine in water to yield 1-{Nα-[1(S)-carboxy-3-phenylpropyl]-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid, a white solid, m.p. 165-166° $[\alpha]_D^{26}$-8-2 (ethanol).

B. Treat 2.45g of the product of Step A with 1.45g of 4-chloro-3-sulfamoylbenzenesulfonyl chloride as described in Example 1D to give the title compound.

Example 6

1-{Nα-[1(S)-Carboxy-3-phenylpropyl]-Nε-[(4-chloro-3-sulfamoyl)benzoyl-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid

Treat 2.45g of th product from Example 5A with 1.1g of 4-chloro-3-sulfamoylbenzoyl chloride as described in Example 2 to give the title compound.

Example 7

1-{N-[1(S)-Carboxy-3-phenylpropyl]-S-[3-(6-chloro-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazinyl-1,1-dioxide) methyl]-(R)-cysteinyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid

A. Stir 10.5g of S-benzyl-L-cysteine and 11.0g og 2-oxo-4-phenylbutyric acid, ethyl ester in 1000ml of absolute ethanol at room temperature for 24 hours. Add. 5.28g of sodium cyanoborohydride and stir the resulting mixture at room temperature for 48 hours. Concentrate this mixture in vacuo at 30°C to give a white residue. Suspend the residue in ice-water, add concentrated hydrochloric acid to maintain pH 2-4, and stir this mixture for 1 1/2-2 hours. Absorb this aqueous solution on XAD-2 (Rohm & Haas Co.) resin. Elute the resin with water and then with absolute ethanol. Concentrate the ethanol solution and chromatograph the residue on a column of silica gel using chloroform : isopropanol : 7% ammonium hydroxide 1:1:1 (organic layer) to give N-[1(S)-carboethoxy-3-phenylpropyl]-S-benzyl-(R)-cysteine.

B. Treat 4.0g of the product of part A and 2.6g of cis,syn-octahydro-1H-indole-2(S)-carboxylic acid, benzyl ester in 10ml of dimethylformamid at 0° under nitrogen with a solution of 2.75g of diphenylphosporylazid in 1.0g of N-methylmorpholine in 10ml of dimethylformamide, and stir at room temperature for 18 hours. Pour the reaction solution into water, adjust to pH 8 with 1N, NaOH, and extract with

ether. Wash the combined ther layers with aqueous sodium chloride solution, dry th ether layer over magnesium sulfate, filter, and concentrate in vacuo to give a residue. Chromatograph this residue on silica gel (60-200 mesh) using hexane : ethylacetate to give 1-{N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-S-benzyl-(R)-cysteinyl}-cis,syn-octahydro-1H-indole-2-(S)-carboxylic acid, benzyl ester.

C. Stir the product of part B in 50ml of a 15-20% solution of hydrobromic in acetic acid under nitrogen for 2 hours, then concentrate to dryness under vacuum at room temperature. Triturate the resultant residue with ether to obtain 1-{N-[1(S)-(ethoxycarbonyl-3-phenylpropyl]-S-benzyl-(R)-cysteinyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid, hydrobromide.

D. React 1.5g of the product from part C in methanol with 3.0ml of 2.5N sodium hydroxide at room temperature for 24 hours and concentrate the resulting mixture in vacuo at room temperature. Absorb the residue on AG 50W-X2 (100-200 mesh, hydrogen form, Bio-Rad) resin. Elute the resin with water and then elute with 4% pyridine in water to yield 1-{N-[1(S)-carboxy-3-phenylpropyl]-S-benzyl-(R)-cysteinyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid, hydrobromide.

E. Treat 1.0g of product form part D with 0.05g of sodium in 100ml of liquid ammonia. Evaporate and concentrate the resulting mixture to give 1-{N-[1(S)-carboxy-3-phenylpropyl]-(R)-cysteinyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid as the sodium salt.

F. React 0.4g of the product from Step E in 20ml of dimethylformamide with 0.36g of 2-bromomethyl-6-chloro-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide

and triethylamine. Concentrate the resulting mixture and chromatograph on an AG 50W-X2 column eluting with 4% pyridine in water to give the title compound.

Example 8

1-{N-[1(R)-Carboxy-2-[S-((3-(6-chloro-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazinyl-1,1-dioxide)methyl))thio]-ethyl]]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid

A. Stir 100g of S-benzyl-L-cysteine ethyl ester hydrochloride, 132g of benzyl pyruvate, and 10g of 3A molecular sieves in 8 liters of ethanol for 18 hours under nitrogen. Add dropwise a solution of 52g of sodium cyanoborohydride in 100ml of ethanol, stir at room temperature for 24 hours, filter, then concentrate the filtrate at room temperature under vacuum. Suspend the resultant residue in 100ml of water and 500ml of ether and adjust the mixture to pH 8 with 1N HCl. Wash the organic layer with saturated sodium chloride solution, dry over sodium sulfate, and filter. Adjust the filtrate to pH 2 with 3M ethereal HCl, decant the supernatant, wash the resulting oily precipitate with 200ml of ether, and mix with saturated aqueous sodium bicarbonate to obtain a solution of pH 8. Extract the mixture with 1 liter of ether, dry the ether layer over sodium sulfate and concentrate at room temperature to give N-[1(R)-carboethoxy-2-(benzylthio)ethyl]-(R,S)-alanine, benzyl ester, an amber oil. Thin layer chromatography in ethyl acetate : hexane (15:85) may b used to separate the two isomers (isom r A at Rf = 0.36, and isomer B at Rf = 0.28), or the proc dur may be continu d on the mixture.

B. Add 50g of th product of part A to 1800ml of a 15-20%

solution of hydrobromic-acetic acid and heat at 50°C for 20 hours. Concentrate the resultant mixture to dryness under vacuum, and wash the resultant oily residue with ether until free of acetic acid to produce N-[1(R)-carboxyethyl-2(benzylthio)ethyl]-(R,S)-alanine hydrobromide, an amber oil.

C. Cool a solution of 50.5g of the product of part B and 33.4g of cis,syn-octahydroindole-2(S)-carboxylic acid benzyl ester in 1 liter of dimethylformamide to 0°C under nitrogen, add dropwise a solution of 35.5g of diphenylphosphorylazide in 1 liter of dimethylformamide, followed by a solution of 33.4g of N-methylmorpholine in 200ml of dimethylformamide, also added dropwise, and stir at room temperature for 18 hours. Pour the reaction solution into 3 liters of water, adjust to pH 8 with 1N NaOH, and extract with 4 x 1 liter of ether. Wash the combined ether layers with 1 liter of aqueous sodium chloride, dry the ether layer over magnesium sulfate, filter, and concentrate under vacuum to an amber oil.

Chromatograph the resultant oil on 2kg of silica gel (60-200 mesh) using ether : hexane (90:10). Collect components having Rf 0.38 and Rf 0.61 as indicated by thin layer chromatography on silica gel eluted with ether. The isomer with Rf 0.61 is 1-{N-[1(R)-carboethoxy-2-(benzylthio)ethyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid, benzyl ester.

D. Stir 0.70g of the (S)-alanyl product of part C and 25ml of a 15-20% solution of hydrobromic-acetic aicd under nitrogen for 2 hours, then concentrate to dryness under vacuum at room temperature. Triturate the resultant residue with ether and filter to obtain 1-{N-[1(R)-carboethoxy-2-(benzylthio)-ethyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid, hydrobromide as a tan solid, m.p. 124-125°C.

E. To a solution of 10.6g of the product of Step D in 500ml of methanol, add 24ml for 2.5N sodium hydroxide solution and stir at room temperature for 24 hours. Concentrate this solution in vacuo and absorb on AG 50W-2 (Bio-Rad) resin (100-200 mesh, hydrogen form). Elute the resin with water and then elute with 4% pyridine in water to yield 1-{N-[1(R)-carboxy-2-(benzylthio)ethyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid.

F. Treat 4.22g of the product of Step E with 0.23g of sodium in 200ml of liquid ammonia. Evaporate the ammonia and absorb the residue on AG 50W-2 (Bio-Rad) resin (100-200 mesh, hydrogen form). Elute the resin with water and then elute with 4% pyridine in water to yield 1-{N-[1(R)-carboxy-2-(mercapto)ethyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid.

G. React 2.2g of the product of Step F in 20ml of dimethylformamide with 2.4g of 3-bromomethyl-6-chloro-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide and triethylamine. Concentrate the resulting mixture to give the title compound.

Example 9

1-{N-[1(S)-Ethoxycarbonyl-5-(4-chloro-3sulfamoyl)-benzenesulfonaminopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid

A. Dissolve 27.0g of ethyl indole-2-carboxylate in 250ml of trifluoroacetic acid. Add 2.05g of platinium oxide, hydrogenate the mixture at 50 lb/in^2 at room temperature. Filter the mixture and concentrate th filtrate in vacuo to give a r sidue. Suspend the r sidue in ether and tr at

with cold dilute sodium hydroxide solution. Dry th organic layer over magnesium sulfate and concentrate it to give ethyl octahydroindole-2-carboxylate, a pale yellow oil.

B. Dissolve 116g of 10-d-camphorsulfonic acid in 1 liter of warm ethyl acetate and add a solution of 86g of the product of part A in 1 liter of ethyl acetate. Allow the mixture to crystallize, heat to reflux, cool to room temperature, and filter. Recrystallize the filter cake from a mixture of 500ml of isopropanol and 1800ml ethyl acetate, filter and dry the crystals to obtain 2-(S)-carboethoxy-cis,syn-octahydro-1H-indole, d-10-camphorsulfonate, m.p. 192-193°C.

C. Slurry 10g of the product of part B in 1 liter of ether, adjust to pH 11 with aqueous sodium hydroxide, and stir for 5 minutes. Wash the organic layer with sodium chloride solution, dry over magnesium sulfate, filter, and evaporate in vacuo at room temperature to obtain 2(S)-carboethoxy-cis,syn-octahydro-1H-indole as a colorless oil. Dissolve the resultant oil in 50ml of methynol containing 23ml of 1N sodium hydroxide, stir at 25°C for 30 minutes, adjust to pH 7 with 1N hydrochloric acid, and evaporate th solvent to give cis,syn-octahydro-1H-indole-2(S)-carboxylic acid.

D. Cool 23ml of benzyl alcohol to 0°C under nitrogen and add 5.95g of thionyl chloride dropwise over 15 minutes, maintaining the temperature at 0°C. Add the product of part C, stir for 1 hour at 0°C, then stir for 24 hours at room temperature. Pour the resulting mixture into 500ml of ether, stir 1 hour under nitrogen, then allow to stand under nitrogen until th solution is clear. Decant th sup r-natant, wash the precipitate with 25ml ether, then slurry the precipitate in 200ml ether and adjust to pH 8-9 with

1N sodium hydroxide. Stir 5 minutes, wash the organic layer with sodium chloride solution, dry over magnesium sulfate, filter and evaporate in vacuo at room temperature to obtain cis,syn-octahydroindole-2(S)-carboxylic acid, benzyl ester as a colorless oil (TLC in ether: one spot, Rf 0.3).

E. To 26g of the product of Step D in 100ml of dichloromethane and 7.8ml of pyridine add 11.0g of pyruvoyl chloride and stir the resulting mixture at room temperature. Extract the reaction mixture with water and dry the organic layer over magnesium sulfate. Concentrate the dichloromethane solution in vacuo and distill the residue to give 1-pyruvoyl-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid, benzyl ester.

F. To 20g of the product from Step E in 400ml of ethanol, add 2.0g of 10% palladium-on-charcoal and hydrogenate at 50 psi at room temperature. Filter ther resulting mixture and concentrate the filtrate in vacuo to give 1-pyruvoyl-cis,syn-octahydro-1H-indole-2(S)carboxylic acid.

G. React 6.20g of Nε-(benzyloxycarbonyl)-L-lysine ethyl ester in 20ml of tetrahydrofuran with 4.8g of 1-pyruvoyl-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid and add 20ml of molecular sieves 4A (Rohm and Haas). Stir the resulting mixture for 4 hours, add 12g of sodium cyanoborohydride in 20ml of methanol and stir the reaction mixture 20 hours. Filter, concentrate to dryness, and partition the residue between water and dichloromethane. Absorb the aqueous phase on strong acidic ion-exchange resin and elute with 4% pyridine in water to give 1-{N-[1(S)-ethoxycarbonyl-5-benzyloxycarbonylaminopentyl]-(R,S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid. Separate the isomers on a column of silica gel using $CHCl_3$: isopropanol : 7% ammonium hydroxide 1:1:1 (organic) as eluant to give 1- N-[1(S)-

htoxycarbonyl-5-benzyloxycarbonylaminopentyl]-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid.

H. Hydrogenate the product from Step G in 300ml of ethanol using 1g of 10% palladium-on-charcoal at 50 psi at room temperature. Filter the mixture and concentrate the filtrate to give 1-{N-[1(S)-ethoxycaronyl-5-aminopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid.

I. React 1.01g of the product of Step H in 20ml of tetrahydrofuran and 0.25g of triethylamine with 0.75g of 4-chloro-3-sulfamoylbenzensulfonyl chloride and stir the resulting mixture at room temperature. Concentrate the resulting mixture in vacuo and chromatograph the residue on a Lobar RP-8 (E. Merck) size B column using acetonitrile : water as eluant to give the title compound.

Example 10

1-{N-[1(S)-Ethoxycarbonyl-5-(4-chloro-3-sulfamoyl-benzamidopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid

Treat 1.01g of 1-{N-[1(S)-ethoxycarbonyl-5-aminopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid, obtained according to Example 9H, in 20ml of tetrahydrofuran and 0.25g of triethylamine with 0.55g of 4-chloro-3-sulfamoylbenzoyl chloride and stir the resulting mixture at room temperature. Concentrate the resulting mixture in vacuo and chromatograph the residue on a Lobar RP-8 (E. Merck) size B column using acetonitrile : water as eluant to give the title compound.

Example 11

1-{N-[1(S)-Carboxy-5-(4-chloro-3-sulfamoyl)benzamidopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid

A. To 4.04g of 1-{N-[1(S)-ethoxycarbonyl-5-aminopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid in 100ml of methanol : water 1:1 add 8ml of 2.5N NaOH at o-5°C and then stir the resulting mixture at room temperature for 24 hours. Concentrate the resulting mixture and absorb on AG 50W-2 (Bio-Rad) resin (100-200 mesh, hydrogen form). Elute the resin with water, and then elute with 4% pyridine in water to yield 1-{N-[1(S)-carboxy-5-aminopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid.

B. React 0.95g of the product from Step 11A with 0.55g of 4-chloro-3-sulfamoylbenzoyl chloride as described in Example 10 to give the title compound.

Example 12

1-{N-[1(S)-Carboxy-5-(4-chloro-3-sulfamoyl)benzenesulfonamidopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid

Treat 0.95g of the product from Example 11A with 0.75g of 4-chloro-3-sulfamoylbenzenesulfonyl chloride as described in Example 9I to give the title compound.

Exampl 13

1-{N-[1(S)-Ethoxycarbonyl-5-(4-chloro-3-sulfamoyl)-benzenesulfonamidopentyl]-(R,S)-alanyl}-(S)-proline

A. Mak a solution of Nε-benzyloxycarbonyl-L-lysine ethyl ester hydrochloride (2.94g) in water (10ml) basic with 15ml of saturated aqueous potassium bicarbonate and extract with CH_2Cl_2. Dry the extract over $MgSO_4$ and concentrate to dryness. Dissolve the residue, Nε-benzyloxycarbonyl-L-lysine ethyl ester, in tetrahydrofuran (20ml) and pyruvoyl-proline (555mg) and add powdered No. 4A molecular sieves (1.0g). Stir the mixture at room temperature for 4 hours. Add sodium cyanoborohydride (630mg) in 1ml of methanol over 2 hours and stir the mixture overnight. Filter the mixtur , concentrate to dryness, and partition the residue between water (10ml) and CH_2Cl_2 (15ml). Absorb the aqueous phase on strong acid ion-exchange resin and elute with 4% pyridin in water to yield 470mg of 1-{N-[1(S)-ethoxycarbonyl-5-benzyloxycarbonylaminopentyl]-(R,S)-alanyl}-S-proline. Remove the protecting group by hydrogenation in ethanol : water 1:1 over 10% Pd/C catalyst at 40 psi. Filter the mixture and take the filtrate to dryness. Chromatograph the residue in methanol on an LH-20 column to give the desired 1-{N-[1(S)-ethoxycarbonyl-5-aminopentyl]-(R,S)-alanyl}-(S)-proline.

B. Condense 0.90g of the product from Step A with 0.75g of 4-chloro-3-sulfamoylbenzenesulfonyl chloride as described in Example 9I to give the title compound.

Example 14

1-{N-[1(S)-Ethoxycarbonyl-5-(4-chloro-3-sulfamoyl)-benzamidopentyl]-(R,S)-alanyl}-(S)-proline

R act 0.90g of the product of Exampl 13A with 0.55g of 4-chloro-3-sulfamoylbenzoylchloride as described in Example 10 to give th title compound.

Example 15

1-{N-[1(S)-Carboxy-5-(4-chloro-3-sulfamoyl)benzenesulfonamidopentyl]-R,S)-alanyl}-(S)-proline

A. Treat 3.50g of the product of Example 13A in 100ml of methanol : water 1:1 with 8.0ml of 2.5N NaOH as described in Example 11A to give 1-{N-[1(S)-carboxy-5-aminopentyl]-(R,S)-alanyl}-(S)-proline.

B. Condense 0.80g of the product of Step A with 0.75g of 4-chloro-3-sulfamoylbenzenesulfonyl chloride as described in Example 9I to give the title compound.

Example 16

1-{N-[(S)-Carboxy-5-(4-chloro-3-sulfamoyl)benzamidopentyl]-(R,S)-alanyl}-(S)-proline

React 0.80g of the product of Example 15A with 0.55g of 4-chloro-3-sulfamoylbenzoyl chloride as described in Example 10 to give the title compound.

Example 17

7-(4-Chloro-3-sulfamoylbenzamido)-2-{N-[1(S)-carboxy-3-phenylpropyl]-(S)-alanyl}-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid

A. Dissolve 1,2,3,4-tetrahydro-7-nitroisoquinoline-3(S)-carboxylic acid ethyl ester (0.1 mole) in ethanol and add the solution to 10% palladium on carbon (1.0g) in a hydrogenation bottle. Hydrogenate the mixture at 30 psi, at

room temperatur until the reduction is complete as indicat d by thin layer chromatography. Remov the catalyst by filtration and evaporate the solvent under reduced pressure to obtain 7-amino-1,2,3,4-tetrahydroisoquinoline-3-(S)-carboxylic acid ethyl ester.

(The preparation of 1,2,3,4-tetrahydro-7-nitroisoquinoline-3(S)-carboxylic acid is described in US patent 4,064,274.)

B. Treat 7-amino-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid ethyl ester (Step A) (0.1 mole) with benzyl alcohol (0.5 mole) and p-toluenesulfonic acid (0.22 mole) in toluene at reflux overnight. Evaporate the solvent under reduced pressure to obtain the p-toluenesulfonic acid salt of the product. Add this salt to aqueous sodium bicarbonate solution with stirring. Extract the mixture with chloroform, dry the extract with magnesium sulfate and evaporate the solvent under reduced pressure to obtain 7-amino-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid benzyl ester.

C. Add a solution of 4-chloro-3-sulfamoylbenzoyl chlorid (0.1 mole) in tetrahydrofuran to a solution of product of Step B in tetrahydrofuran containing triethylamine (0.1 mole). When the reaction is complete as indicated by thin layer chromatography, remove the triethylamine hydrochloride by filtration and evaporate the solvent at reduced pressure. Purify the residue by chromatography to obtain 7-(4-chloro-3-sulfamoylbenzamido)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid benzyl ester.

D. Cool a solution of N-[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanine (0.01 mole) and the benzyl ester (0.01 mole) from Step C in dry dimethylformamide to 0°C. Add N-m thylmorpholine (0.01 mole) with stirring, then add dropwise,

with stirring, a solution of diphenylphosphoryl azide (0.01 mol) in dry dimethylformamide while maintaing the temperature at 0°C. Stir the reaction for one hour at 0°C and overnight at room temperature. Dilute the mixture with ethyl acetate and wash with aqueous sodium bicarbonate. Dry the organic solution with magnesium sulfate and evaporate the solvent under reduced pressure. Purify the residu by chromatography to give 7-(4-chloro-3-sulfamoylbenzamido)-2-{N-[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanyl}-1,2,3,4-tetrahydroisoquinoline-3-(S)-carboxylic acid benzyl ester.

E. Add a solution of 0.01 mole of the benzyl ester from Step D in ethanol to 10% palladium on charcoal (0.5g) in a hydrogenation bottle. Hydrogenate the mixture at 60 psi, at room temperature until removal of benzyl group is complete as indicated by thin layer chromatography. Remove the catalyst by filtration and evaporate the solvent under reduced pressure to obtain 7-(4-chloro-3-sulfamoylbenzamido)-2-{N-[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanyl}-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid.

F. Stir a solution of 0.01 mole of the product from Step E in water containing sodium hydroxide (0.022 mole) at room temperature until the reaction is complete as indicated by thin layer chromatography. Add methanol to the reaction and then add 0.022 equivalents of Dowex-50(H+) with stirring. Remove the resin by filtration and evaporate the solvent under reduced pressure. Purify the product by chromatography to obtain the title compound.

Example 18

7-(4-Chloro-3-sulfamoylbenzenesulfonamido)-2-{N-[1(S)-carboxy-3-phenylpropyl]-(S)-alanyl}-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid

A. Follow the procedure of Example 17C using 4-chloro-3-sulfamoylbenzenesulfonyl chloride in place of 4-chloro-3-sulfamoylbenzoyl chloride to obtain 7-(4-chloro-3-sulfamoylbenzoyl chloride to obtain 7-(4-chloro-3-sulfamoylbenzenesulfoamido)-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid benzyl ester.

B. Couple the product from Step A with N-[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanine following the procedure of Example 17D. Chromatograph the crude product to obtain 7-(4-chloro-3-sulfamoylbenzenesulfonamido)-2-{N-[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanyl}-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid benzyl ester.

C. Subject the benzyl ester from Step B to hydrogenolysis as described in Example 17E to obtain 7-(4-chloro-3-sulfamoylbenzenesulfonamido)-2-{N-[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanyl}-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid.

D. Treat the product from Step C with aqueous sodium hydroxide followed by Dowex-50(H+) as described in Example 17F to obtain the title compound.

Example 19

5-(4-Chloro-3-sulfamoylbenzamido)-1-{N-[1(S)-carboxy-2-phenylpropyl]-(S)-alanyl}-octahydro-1H-indole-2-carboxylic acid

A. Following the procedure of Example 17A, substitute 5-nitroindole-2-carboxylic acid ethyl ester for 1,2,3,4-tetrahydro-7-nitroisoquinoline-3(S)-carboxylic acid ethyl ester to obtain 5-aminoindole-2-carboxylic acid ethyl ester.

B. Dissolve 5-aminoindole-2-carboxylic acid ethyl ester in trifluoroacetic acid containing PtO_2. Hydrogenate at 60 psi on a Parr shaker for 24 hours. Distill the trifluoroacetic acid at reduced pressure and dissolve the residue in ethyl acetate. Filter and adjust to pH 9 with 1N NaOH. Dry the organic layer over $MgSO_4$ and distill the solvent at reduced pressure to obtain 5-aminooctahydro-1H-indole-2-carboxylic acid ethyl ester.

C. Following the procedure of Example 17B, substitute 5-aminooctahydro-1H-indole-2-carboxylic acid ethyl ester for 7-amino-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid ethyl ester to obtain 5-aminooctahydro-1H-indole-2-carboxylic acid benzyl ester.

Analogously following the procedures of Examples 17C, 17D, 17E and 17F obtain 5-(4-chloro-3-sulfamoylbenzamido)octahydro-1H-indole-2-carboxylic acid benzyl ester,
5-(4-chloro-3-sulfamoylbenzamido)-1-{N-[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanyl}-octahydro-1H-indole-2-carboxylic acid benzyl ester,
5-(4-chloro-3-sulfamoylbenzamido)-1-{N-[1(S)-carbo thoxy-3-phenylpropyl]-(S)-alanyl}-octahydro-1H-indole-2-carboxylic acid and the title compound.

Example 20

5-(4-Chloro-3-sulfamoylbenzenesulfonamido)-1-{N-[1(S)-carboxy-3-phenylpropyl]-(S)-alanyl}-octahydro-1H-indole-2-caroxylic acid

A. Following the procedures of Example 18A, substitute 5-aminooctahydro-1H-indole-2-carboxylic acid benzyl ester for 7-amino-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid benzyl ester and 4-chloro-3-sufamoylbenzenesulfonyl chloride for 4-chloro-2-sulfamoylbenzoyl chloride to obtain 5-(4-chloro-3-sulfamoylbenzenesulfonamido)-octahydro-1H-indole-2-carboxylic acid benzyl ester.

B. Following the procedures of Examples 17D, 17E and 17F obtain 5-(4-chloro-3-sulfamoylbenzenesulfonamido)-1-{N-[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanyl}-octahydro-1H-indole-2-caroxylic acid benzyl ester, 5-(4-chloro-3-sulfamoylbenzenesulfonamido)-1-{N-[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanyl}-octahydro-1H-indole-3-carboxylic acid and the title compound.

Example 21

1-{N-[1(S)-Ethoxycarbonyl-5-(4-chloro-3-sulfamoyl-benzamido)pentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid hydrochloride

A. N-[1(S)-ethoxycarbonyl-5-(benzyloxycarbonylamino) pentyl]-(S)-alanine.

Dissolve 17g of N-[1(S)-ethoxycarbonyl-5-(benzyloxy-carbonylamino)pentyl]-(S)-alanine, t-butyl ester in 150ml of trifluoroacetic acid at 5°C. Stir at room temperature for .5hr. and then c ncentrate at room temp rature in vacuo.

Triturate the residue with th r and dry under vacuum to give the title compound.

B. 1-{N-[1(S)-ethoxycarbonyl-5-(benzyloxycarbonylamino)-pentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid benzyl ester.

In 5ml of DMF, dissolve 0.7g of N-[1(S)-ethoxycarbonyl-5-(benzyloxycarbonylamino)pentyl]-(S)-alanine, 0.325g of cis,syn-octahydro-1H-indole-2(S)-carboxylic acid benzyl ester, 0.24g of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride, and 0.20g of 1-hydroxybenzo-triazole. Stir this solution under nitrogen for 18 hr. and then concentrate at room temperature in vacuo. Partition between ether and water. Dry the organic layer ($MgSO_4$) and concentrate at room temperature in vacuo to give the title compound.

C. 1-{N-[1(S)-ethoxycarbonyl-5-aminopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid.

In 80ml of ethanol dissolve 3.7g of 1-{N-[1(S)-ethoxy-carbonyl-5-(benzyloxycarbonylamino)pentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid benzyl ester. To this add 1g of 20% palladium hydroxide on carbon. Hydrogenate this mixture at 60 psi for 18 hr. Filter and concentrate at room temperature in vacuo. Triturate the oily residue with ether and filter to give the title compound, m.p. 160°C (decomp.), $[\alpha]_D^{26}$-40.7° (MEOH).

D. 1-{N-[1(S)-ethoxycarbonyl-5-(4-chloro-3-sulfamoyl-benzamido)pentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indol -2(S)-carboxylic acid hydrochloride.

Dissolve 0.7g of 1-{N-[1(S)-ethoxycarbonyl-5-aminopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indol -2(S)-carb xylic acid and 0.4g of triethyl amine in 40ml of tetrahydro-

furan and cool to 5°C. To this solution add dropwis a solution of 0.48g of 4-chloro-3-sulfamoylbenzoyl chlorid in 20ml of tetrahydrofuran. Stir for 1 hr. at 5°C and 1 hr. at 25°C. Filter and concentrate in vacuo. Dissolve the residue in 200ml of dichloromethane and acidify with HCl-gas. Decant and triturate the residue several times with dichloromethane to give the title compound, m.p. 185°C, $[\alpha]_D^{26}$ -20° (MEOH).

Example 22

1-{N-[1(S)-Ethoxycarbonyl-5-(4-chloro-3-sulfamoylbenzamido)pentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid

A. N-[1(S)-ethoxycarbonyl-5-(benzyloxycarbonylamino) pentyl]-(S)-alanine, t-butyl ester.

Dissolve 60g of Nε-benzyloxycarbonyl-(S)-lysine, ethyl ester and 90g of t-butyl bromopropionate and 22g of triethylamine in 200ml of DMF. Heat this soution at 70°C for 18 hr. Concentrate in vacuo and dissolve the residu in ethyl acetate. Wash organic layer with water and brine. Dry organic layer ($MgSO_4$) and concentrate in vacuo. Chromatograph the residue on silica gel (100-200 mesh) using ether : hexane (1:1) as solvent. Elute SR-isomer and then the title compound. Thin layer chromatography in ether : hexane 1:1 shows the SR-isomer at 0.2 and the SS-isomer at 0.1

B. N-[1(S)-ethoxycarbonyl-5-aminopentyl]-(S)-alanin t-butyl ester.

Dissolve 10g of N-[1(S)- thoxycarbonyl-5-(benzyloxycarbonylamino)pentyl]-(S)-alanine, t-butyl ester in 40ml of ethanol. Add 3.0g of 20% palladium hydroxide on

carbon. Hydrogenate at 60 psi for 18 hr. Filter and concentrate in vacuo to give title compound.

C. N-[1(S)-ethoxycarbonyl-5-(4-chloro-3-sulfamoylbenzamido)pentyl]-(S)-alanine, t-butyl ester.
Dissolve 1.0g of N-[1(S)-ethoxycarbonyl-5-aminopentyl]-(S)-alanine, t-butyl ester in 50ml of THF. Add 0.3g of triethylamine. Cool to 5°C under nitrogen. Add, dropwise, with stirring a solution of 0.8g of 4-chloro-3-sulfamoyl benzoyl chloride in 30ml of THF. Warm to room temperature and stir for 10 hr. Filter and concentrate in vacuo. Dissolve residue in ethyl acetate and wash with water and brine. Dry organic layer ($MgSO_4$) and concentrate in vacuo to give the title compound. Purify by chromatography on silica gel using ethyl acetate as eluant.

D. N[1(S)-ethoxycarbonyl-5-(4-chloro-3-sulfamoylbenzamido)pentyl]-(S)-alanine, hydrochloride.
Dissolve 0.75g of N-[1(S)-ethoxycarbonyl-5-(4-chloro-3-sulfamoylbenzamido)pentyl]-(S)-alanine, t-butyl ester in 10ml of dioxane saturated with HCl gas. Keep at room temperature 18 hr. Concentrate in vacuo and triturate the residue with ether to give title compound.

E. 1-{N-[1(S)-ethoxycarbonyl-5-(4-chloro-3-sulfamoylbenzamido)pentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid, benzyl ester.
In 20ml of DMF dissolve 0.75g of N-[1(S)-ethoxycarbonyl-5-(4-chloro-3-sulfamoylbenzamido)pentyl-(S)-alanine HCl, 0.39g of cis,syn-octahydro-1H-indole-2(S)-carboxylic acid benzyl ester, 0.40g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl, 0.23g of 1-hydroxybenzotriazole and 0.15g of N-m thyl morpholin . Stir under nitrogen for 18 hr., concentrate at room temperature (0.03 mm) and partition residu between ethyl acetat and water. Dry organic

layer ($MgSO_4$) and concentrate in vacuo to give an oil. Chromatograph the oil on silica gel using ethyl acetate as eluant to give the title compound.

F. 1-{N-[1(S)-ethoxycarbonyl-5-(4-chloro-3-sulfamoylbenzamido)pentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid.

Dissolve 0.05g of 1-{N-[1(S)-ethoxycarbonyl-5-(4-chloro-3-sulfamoylbenzamido)pentyl-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid benzyl ester in 5ml of 20% HBr in glacial acetic acid and allow to stand for 4 hr. Concentrate at room temperature(0.03 mm) and triturate with ether to yield product in the form of its hydrobromide salt. Generate the free base by dissolving the hydrobromide salt in 20% aqueous ethanol and absorbing on a strongly acidic ion exchange column (Bio-Rad AG 50w-X2). Elute with pyridine : water 4:96 and concentrate eluant in vacuo to yield title compound. Generate HCl salt of title compound by adding title compound to dichloromethan and HCl gas to give title compound in the form of its hydrochloride. m.p. 185°C $[\alpha]_D^{26}$ -20° (MEOH).

Example 23

Treat the benzyl ester from example 17-C with N-carbobenzoxy-alonine-N-hydroxysuccinimide ester (0.10 mole) in cimethylformamide at room temperature. When the reaction is complete as indicated by thin layer chromatography, evaporate the solvent at reduced pressure. Add ethyl acetate and wash with aqueous sodium bicarbonate solution. Dry the organic solution with magnesium sulfate and evaporate the solvent at reduced pressure. Purify the residue by chromatography. Dissolve this product in ethanol and add the solution to 10% palladium on charcoal (1.0g) in a hydrogenation bottle. Hydrogenate the mixture at 30 psi, until the reaction is complete as indicated by thin layer chromatography. Filter the mixture and evaporate the solvent at reduced pressure to give 7-(4-chloro-3-sulfamoylbenzamido)-2-[(S)-alanyl]-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid. Dissolve 7-(4-chloro-3-sulfamoylbenzamido)-2-[(S)-alanyl]-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid (0.10 mole) in 100ml of absolute ethanol and add 2-oxo-4-phenylbutyric acid, ethyl ester (0.30 mole). Add 50ml of 3 Angstrom molecular sieve pellets and stir the resulting mixture at room temperature for 18 hrs. Filter the mixture and treat the filtrate with sodium cyanoborohydride (0.30 mole) at room temperature for 2 hrs. Concentrate the mixture under reduced pressure, dilute the oil with dilute hydrochloric acid and stir at room temperature for one hour. Absorb the aqueous solution on XAD-2 resin (Rohm & Haas Co.). Elute the resin with water and then with m thanol. Concentrate the m thanol solution and purify the residue by chromatography to obtain

7-(4-Chloro-3-Sulfamoylbenzamido)-2- N-[1(S)-Carboethoxy-3-Phenylpropyl]-(S)-Alanyl -1,2,3,4-Tetrahydroisoquinoline-3-(S)-Carboxylic Acid

Example 24

Add ethyl 2-bromo-4-phenylbutanoate (0.10 mole) to a solution of 7-(4-chloro-3-sulfamoylbenzamido-2-[(S)-alanyl]-1,2,3,4-tetrahydrosioquinoline-3(S)-carboxylic acid (0.10 mole) and triethylamine (0.20 mole) in 200ml of dimethylformamide and heat the mixture at 70°C for 18 hrs. Remove the solvent at reduced pressure and purify the residue by ion-exchange chromatography to give the product as a mixture of diostereoisomers. Purify this mixture by chromatography to obtain 7-(4-Chloro-3-Sulfamoylbenzamido)-2- N-[1(S)-Carboethoxy-3-Phenylpropyl]-(S)-Alanyl -1,2,3,4-Tetrahydroisoquinoline-3-(S)-Carboxylic Acid

Example 25

1-{N-[1(S)-ethoxycarbonyl-5-[3-hydroxy-3-(4-chloro-3-sulfamoylphenyl)phthalimidine-2-yl]pentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S) carboxylic acid.

Dissolve 3.4g (0.01 mole) of 3-hydroxy-3-(4-chloro-3-sulfamylphthalilimidine, 4g (0.01 mole) of 1-{N-[1(S)-ethoxycarbonyl-5-amino-pentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2-(S) carboxylic acid and 2g (0.01g) of p-toluenesulfonic acid monohydrate in 10ml of N,N-dimethylformamide. Stir at 25°C for 2 days then concentrate at room temperatur under vacuum. Chromatograph the crude product on an acid ion exchang column (Dowex-50) using water followed by 4% aqu ous pyridine followed by chromatography on Sephadep LH-20 (m thanol) to obtain the product.

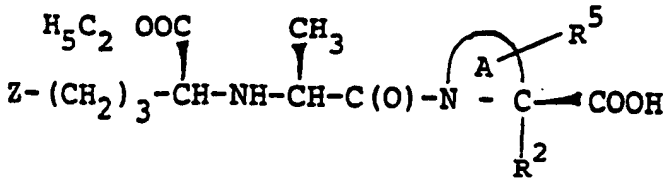
Example 26

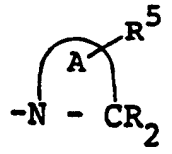
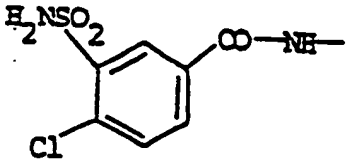
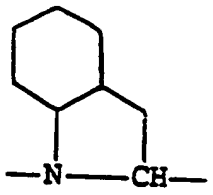
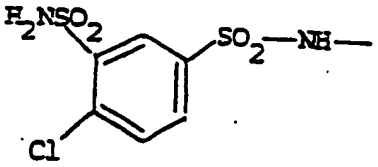
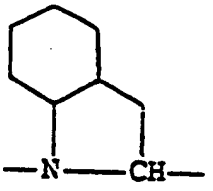
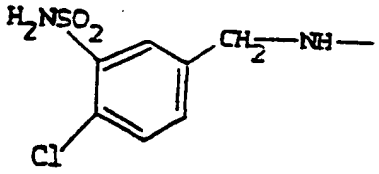
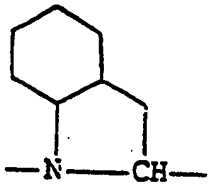
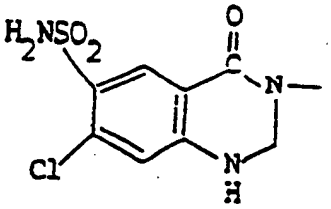
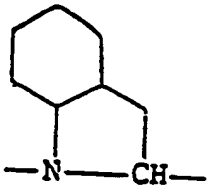
1-{N-[1(S)-ethoxycarbonyl-5-[7-chloro-4-oxo-6-sulfamyl-2-phenyl-1,2,3,4-tetrahydro quinazolin-3-yl]pentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S) carboxylic acid hydrochloride.

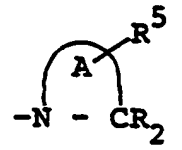
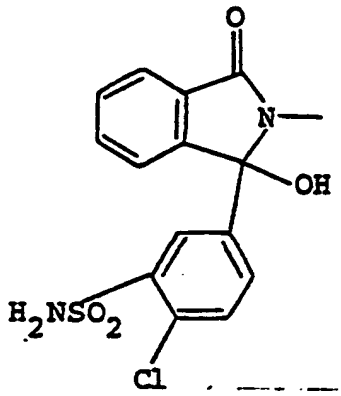
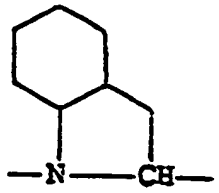
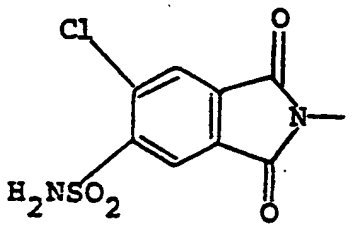
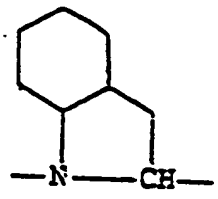
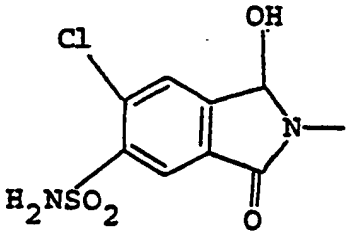
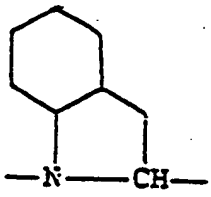
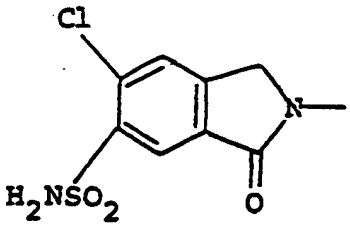
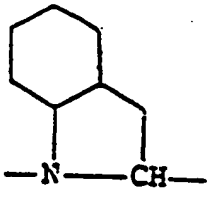
Dissolve 3.8g (0.01 mole) of 6-chloro-7-sulfamyl-isotoic anhydride and 4g (0.01 mole) of 1-{N-[1(S)-ethoxycarbonyl-5-aminopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2-(S)-carboxylic acid in 20ml of pyridine. Stir mixture until gas evolution stops (3 hrs). Concentrate at room temperature under vacuum. Chromatograph the crude product on an acid ion exchange column (Dowex-50) using water followed by 4% aqueous pyridine to obtain 1-{N-[1(S)-ethoxycarbonyl-5-[[4-chloro-2-amino-5-sulfamylphenyl)carbonyl]amino]pnetyl]-(S)alanyl}-cis,syn-octahydro-1H-indole-2(S) carboxylic acid. HCl salt m.p. 180°C(d) $[\alpha]_D^{26}$=-16.6° (methanol C= 0.7)

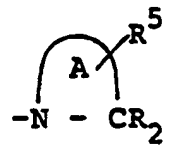
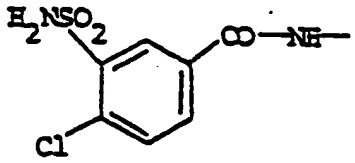
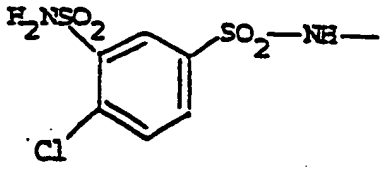
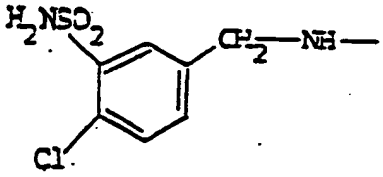
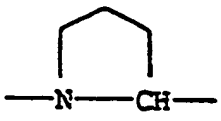
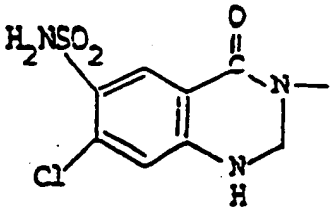
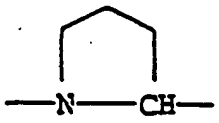
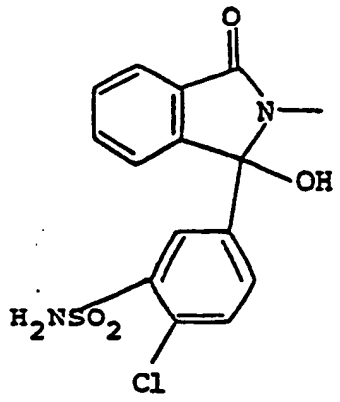
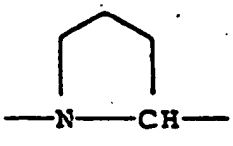
Dissolve the above intermediate in 20ml of acetic acid and add 2g (0.02 mole) of benzaldehyde. Stir for 3 days and concentrate at room temperature under vacuum. Chromatograph the residue on a strong acid on exchange column (Dwex-50) using water followed by 4% aqueous pyridine. Concentrate under vacuum and dissolve the residue in ethanol ether. Crudify with HCl gas and dilute with ether to cause the product to precipitate as a white solid. m.p. 180°C(d)

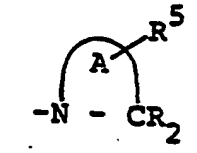
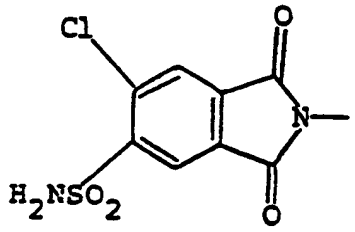
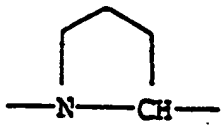
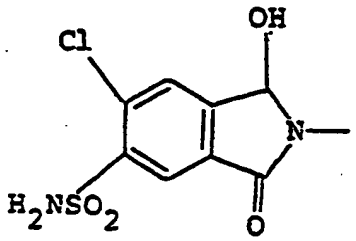
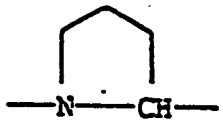
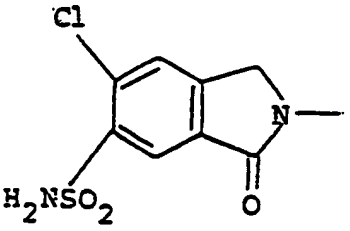
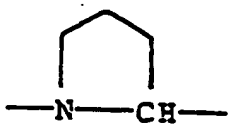
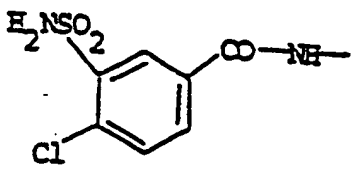
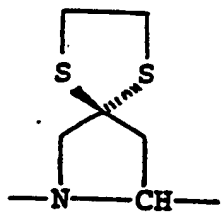
Th following compounds exemplify the compounds of formula I, which can be prepared according to the described processes and the examples. Other est rs and th corresponding free acids ar equally important.

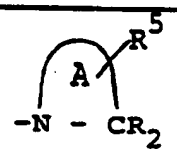
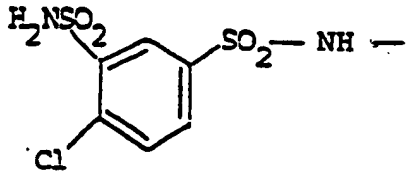
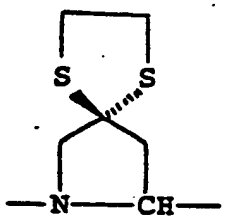
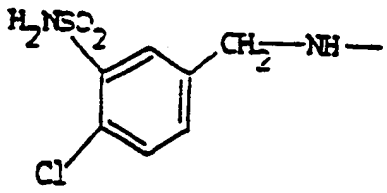
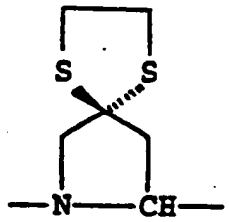
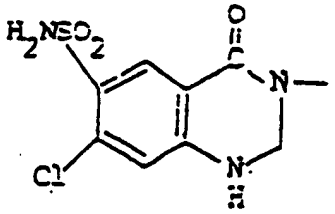
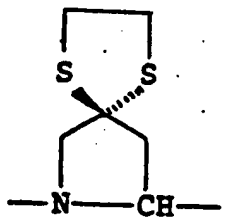
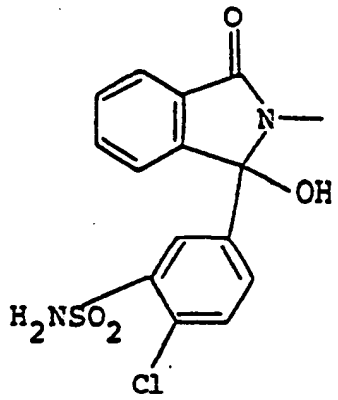
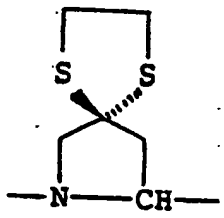
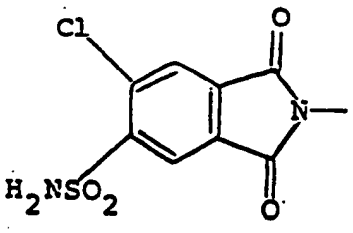
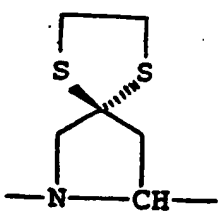


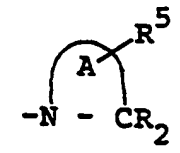
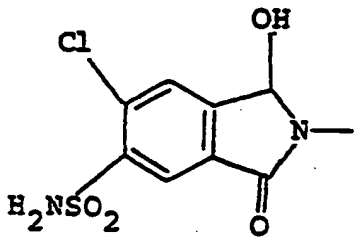
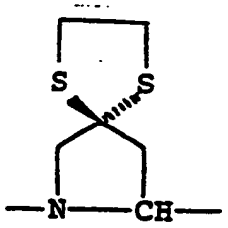
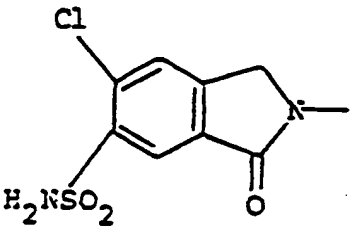
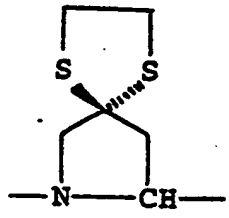
No.	Z	
1		
2		
3		
4		

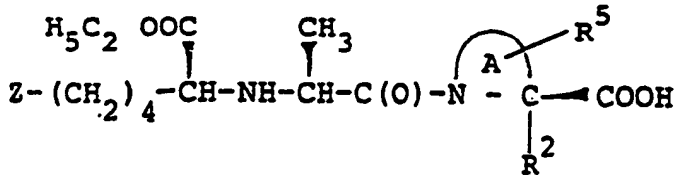
No.	Z	
5		
6		
7		
8		

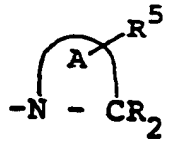
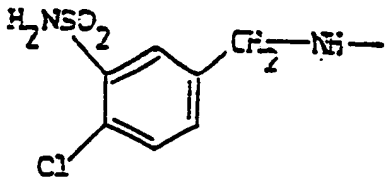
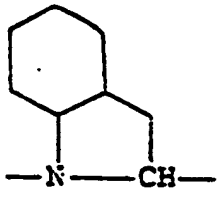
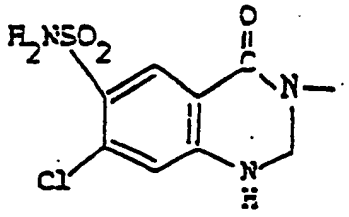
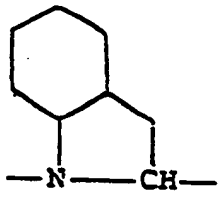
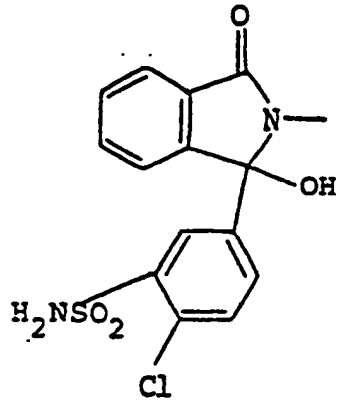
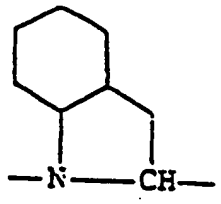
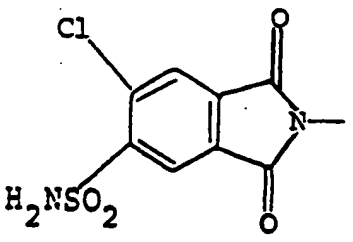
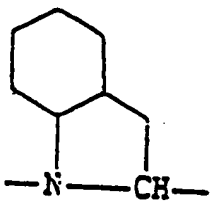
No.	Z	
9		
10		
11		
12		
13		

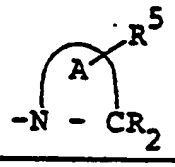
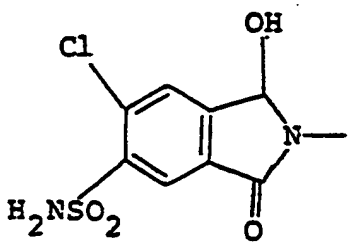
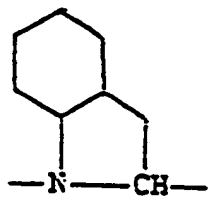
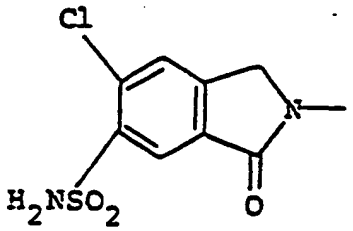
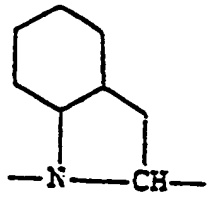
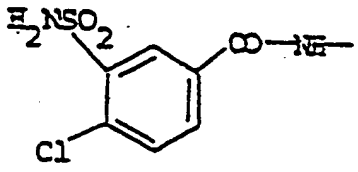
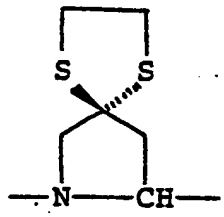
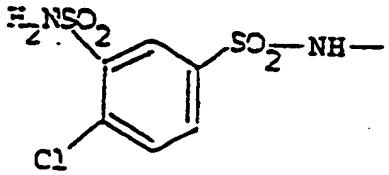
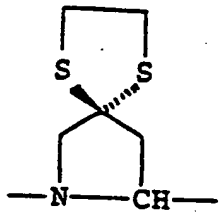
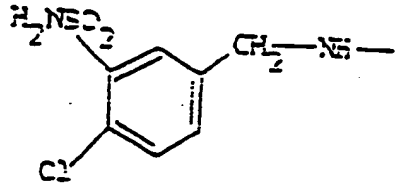
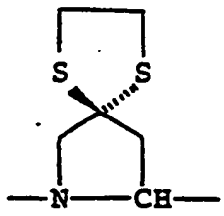
No.	Z	
14		
15		
16		
17		

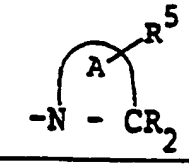
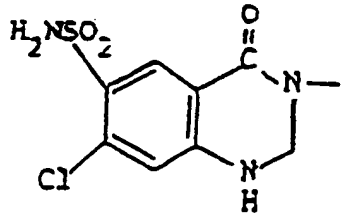
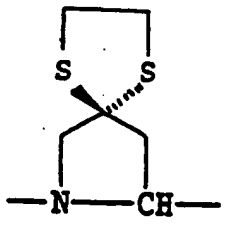
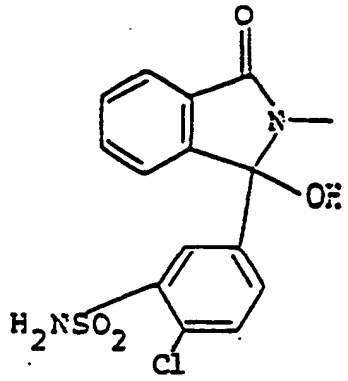
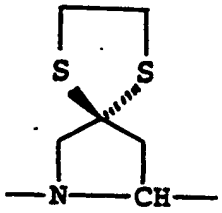
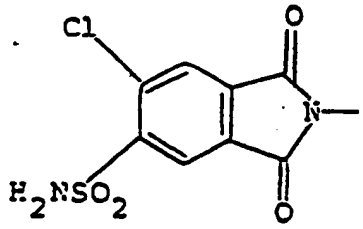
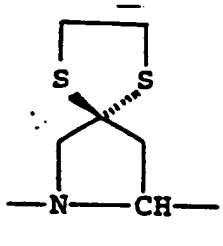
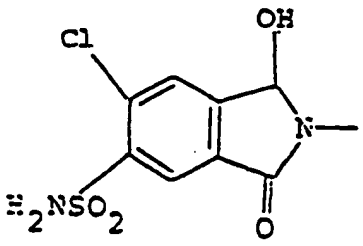
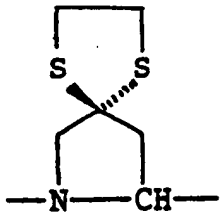
No.	Z	
18		
19		
20		
21		
22		

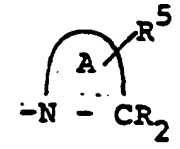
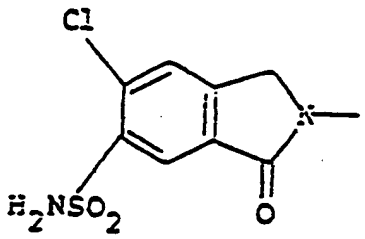
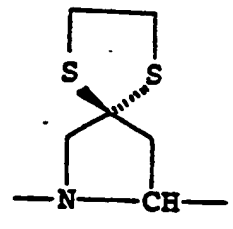
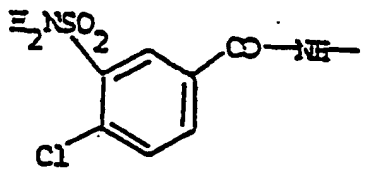
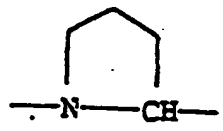
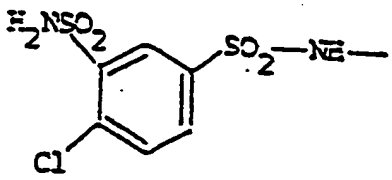
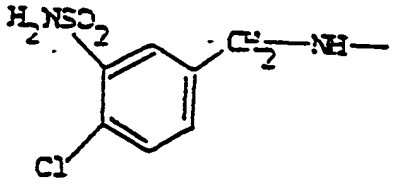
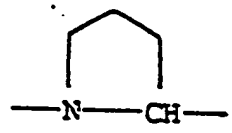
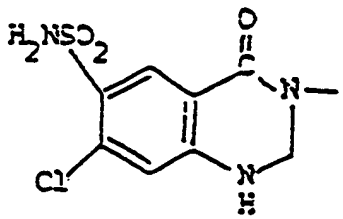
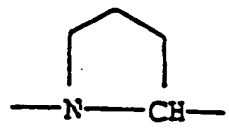
No.	Z	
23		
24		

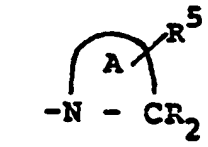
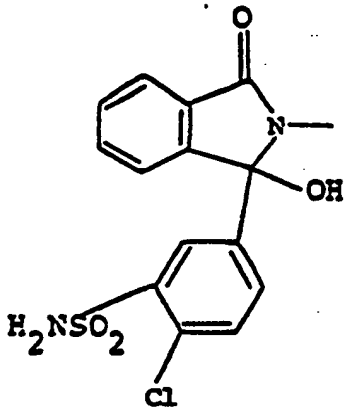
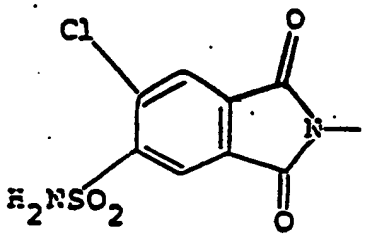
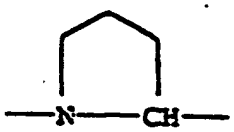
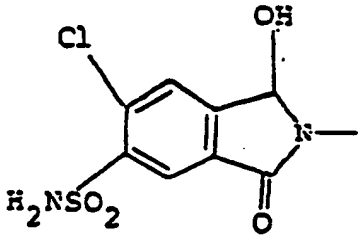
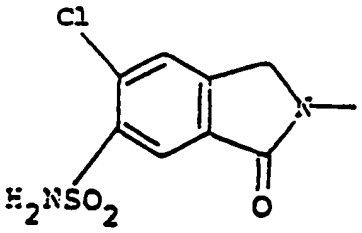


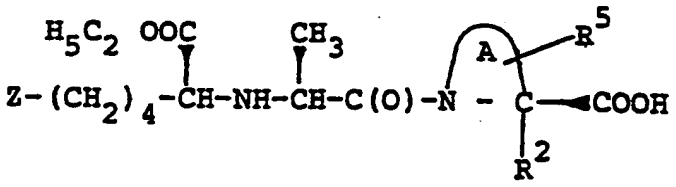
No.	Z	
25		
26		
27		
28		

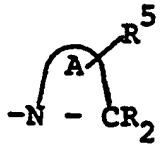
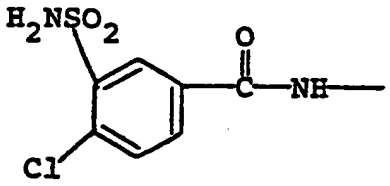
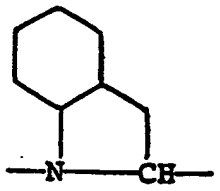
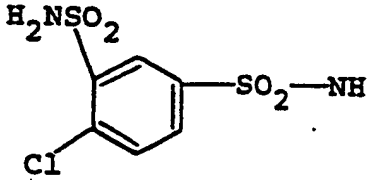
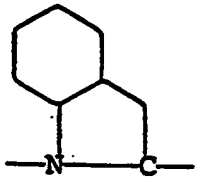
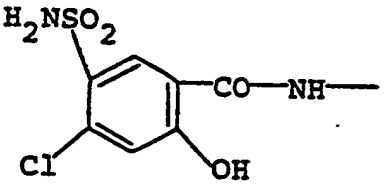
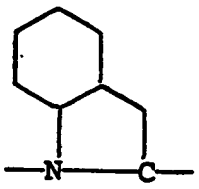
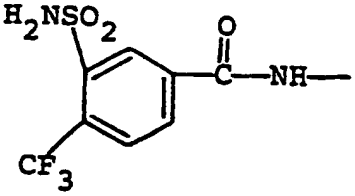
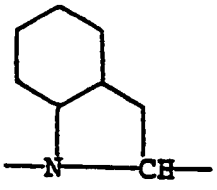
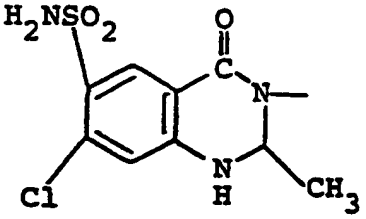
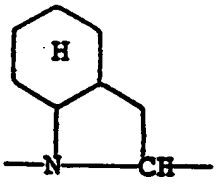
No.	Z	
29		
30		
31		
32		
33		

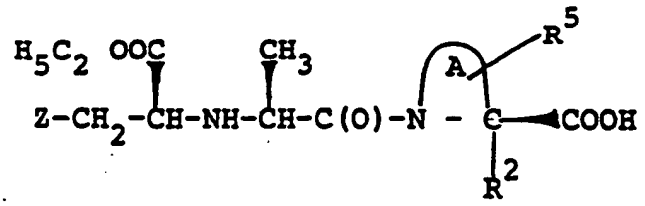
No.	Z	
34		
35		
36		
37		

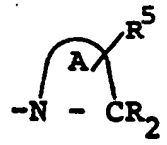
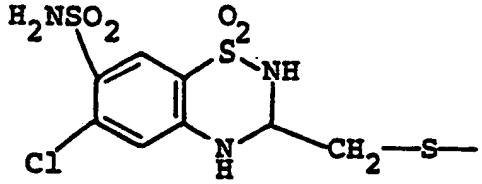
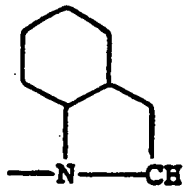
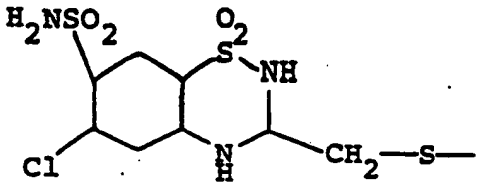
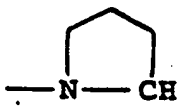
No.	Z	
38		
39		
40		
41		
42		

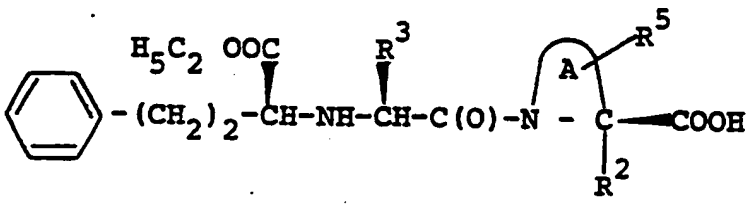
No.	Z	
43		
44		
45		
46		

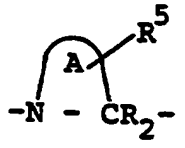
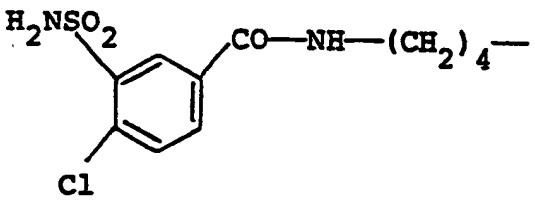
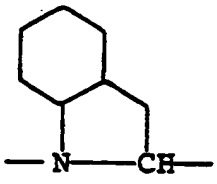
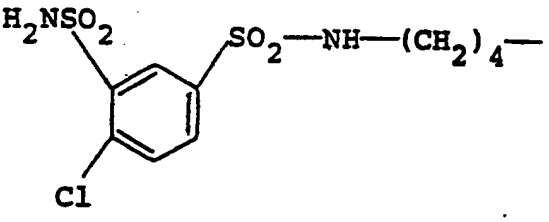
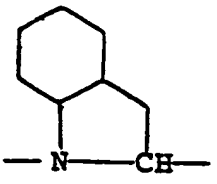
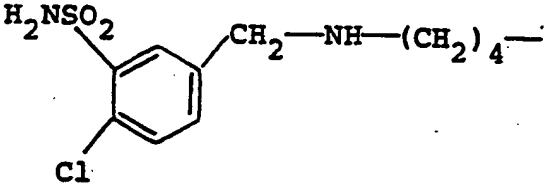
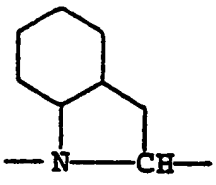
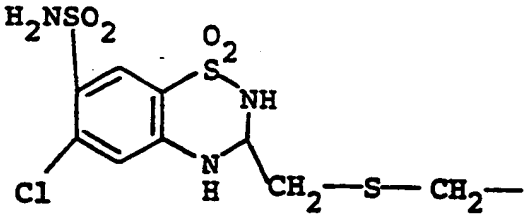
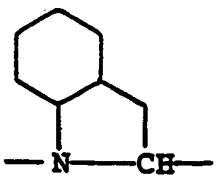


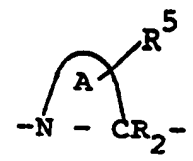
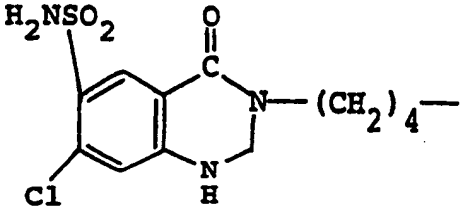
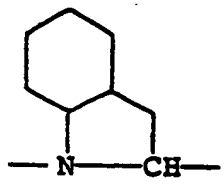
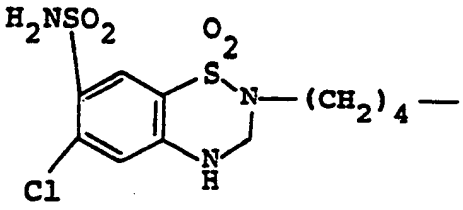
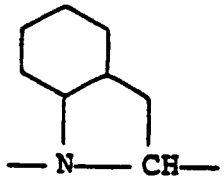
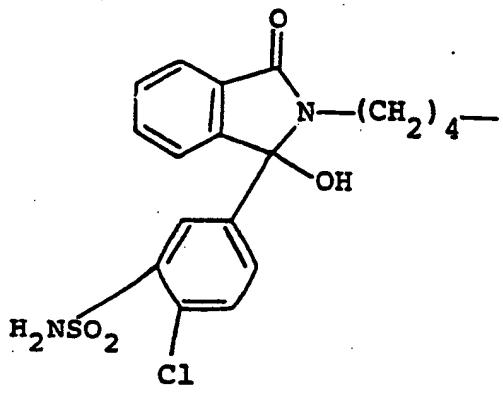
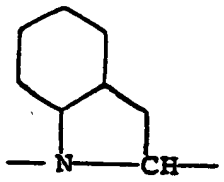
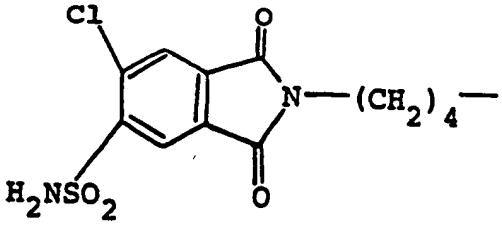
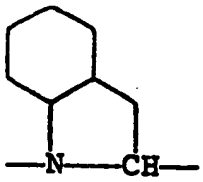
No.	Z	
47		
48		
49		
50		
51		

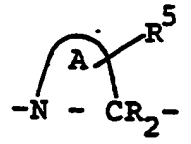
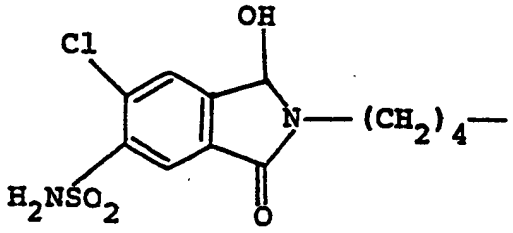
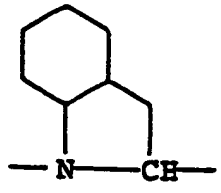
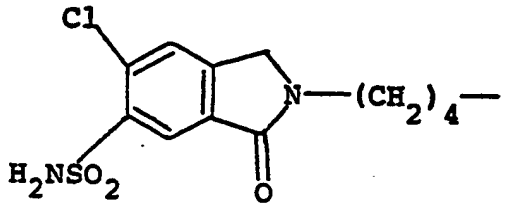
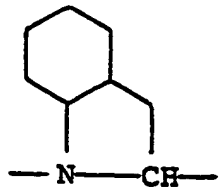
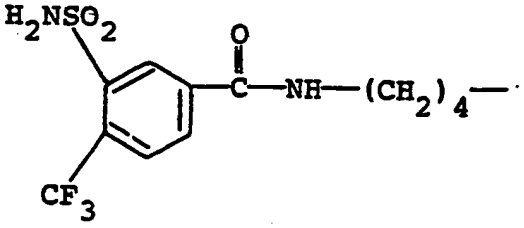
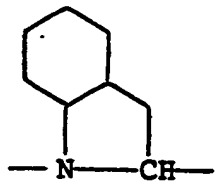
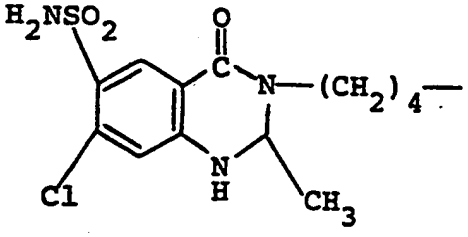
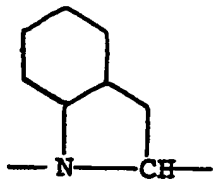
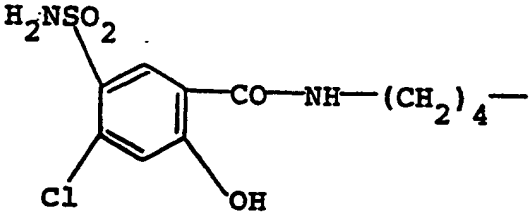
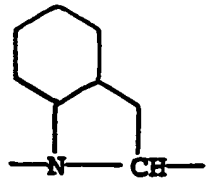


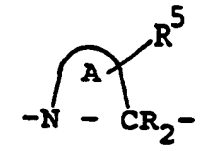
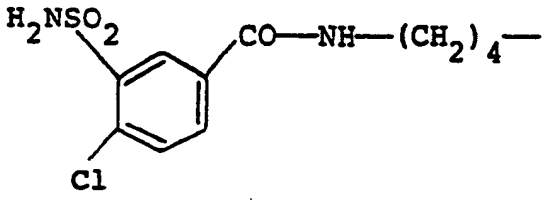
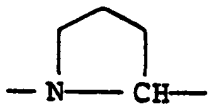
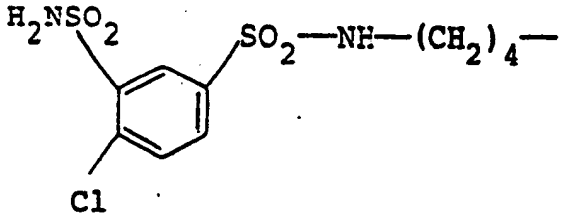
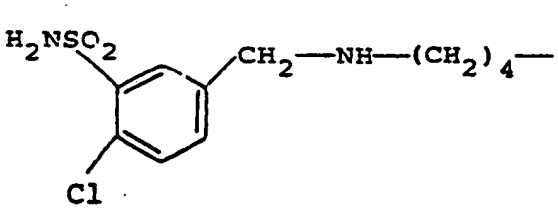
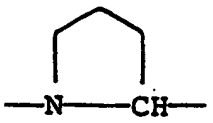
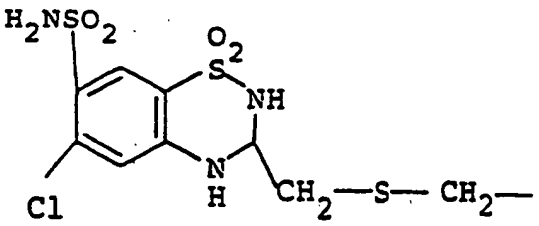
No.	Z	
52		
53		

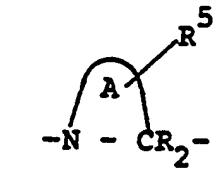
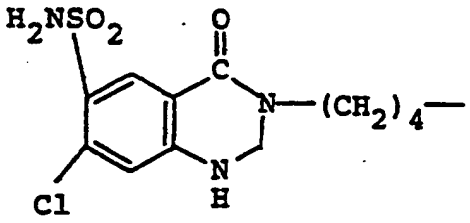
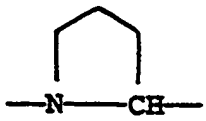
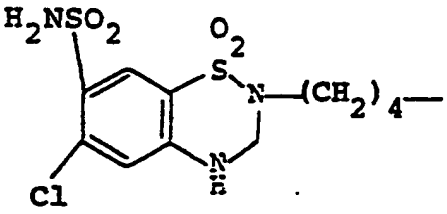
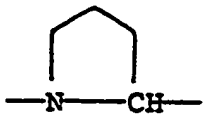
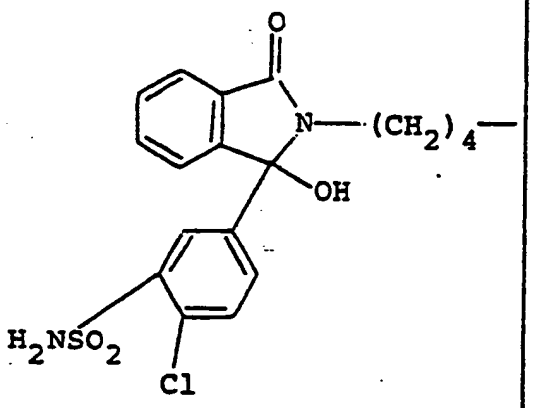
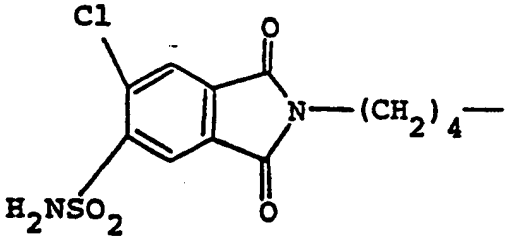


No.	R^3	
54		
55		
56		
57		

No.	R^3	
58		
59		
60		
61		

No.	R^3	
62		
63		
64		
65		
66		

No.	R^3	
67		
68		
69		
70		

No.	R^3	
71		
72		
73		
74		

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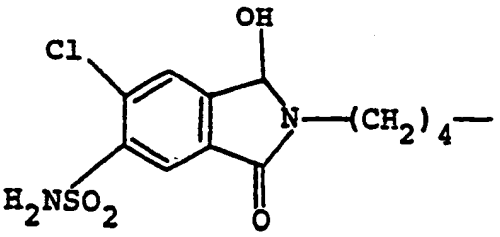
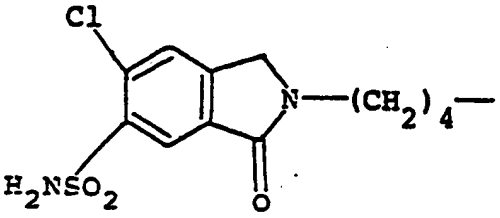
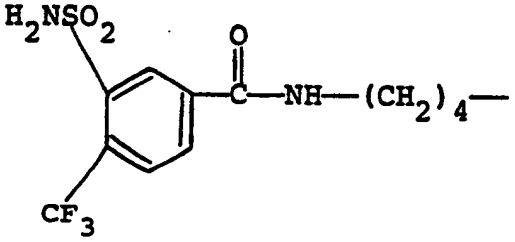
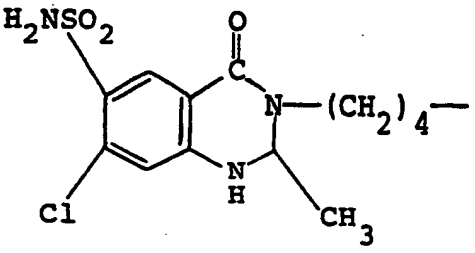
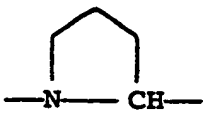
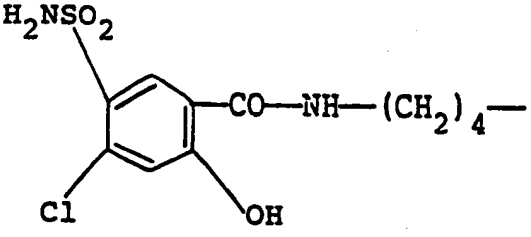
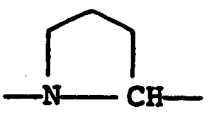
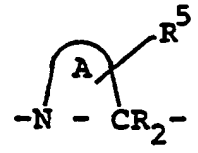
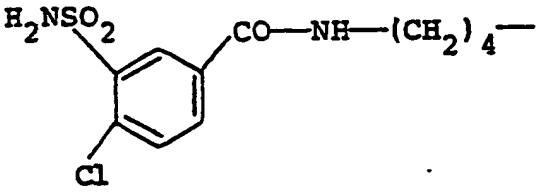
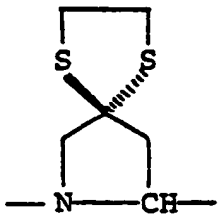
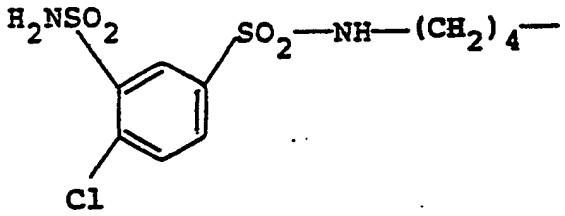
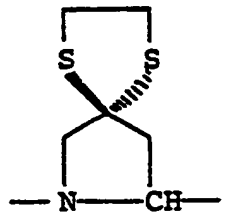
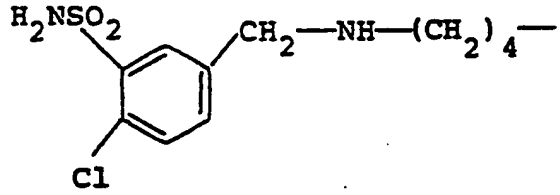
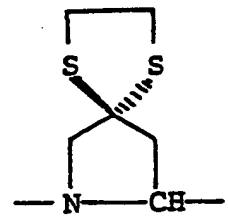
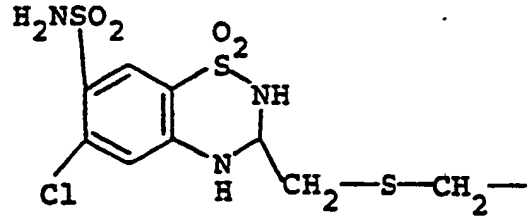
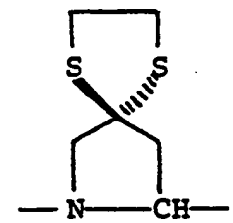
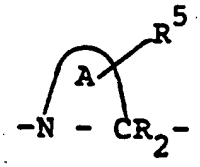
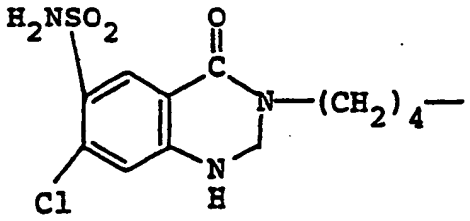
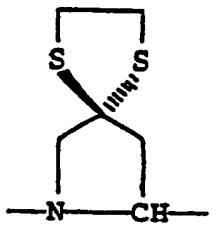
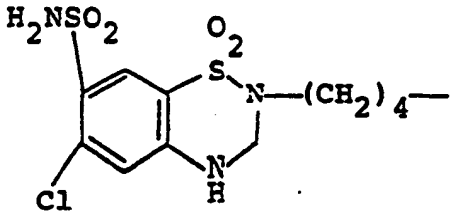
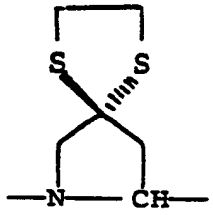
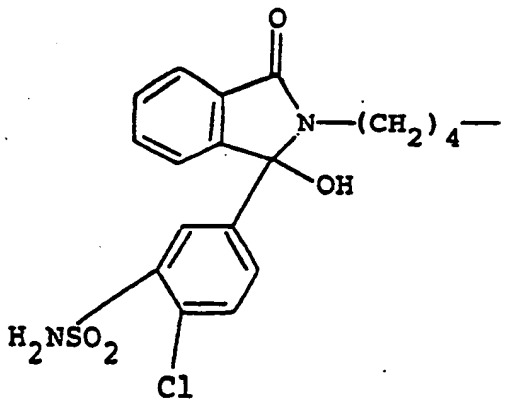
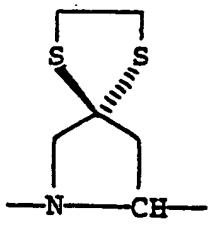
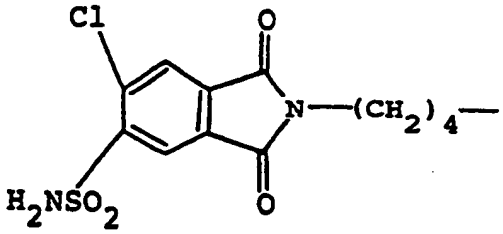
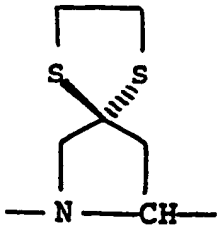
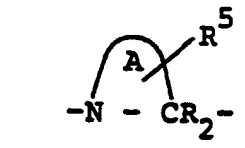
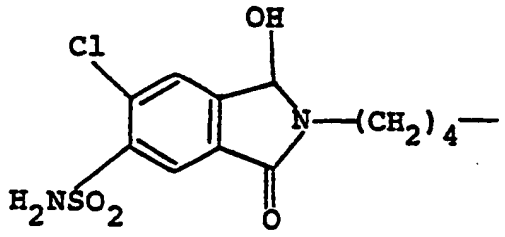
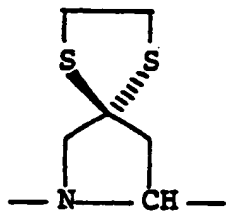
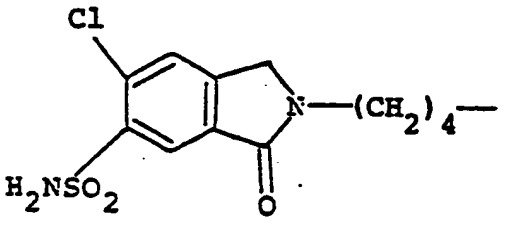
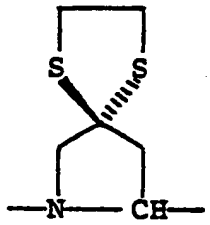
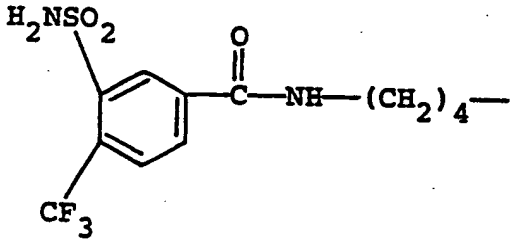
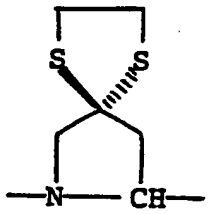
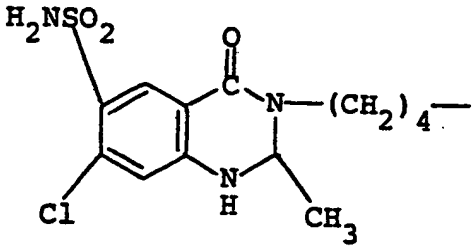
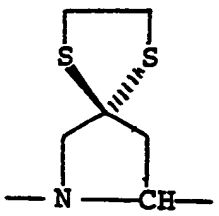
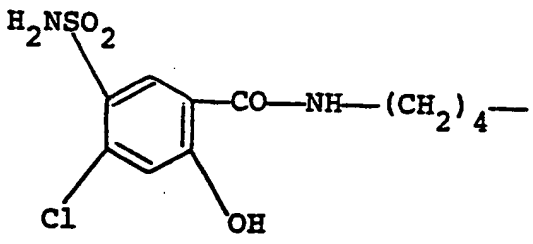
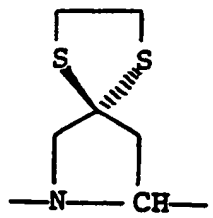
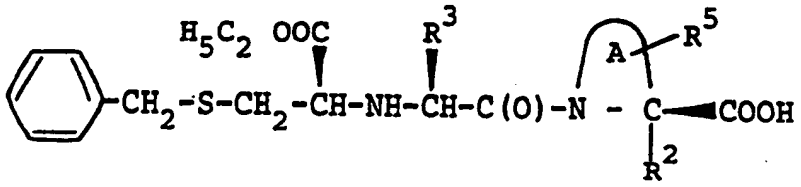
75		
76		
77		
78		
79		

No.	R^3	
80		
81		
82		
83		

No.	R^3	
84		
85		
86		
87		

No.	R^3	
88		
89		
90		
91		
92		



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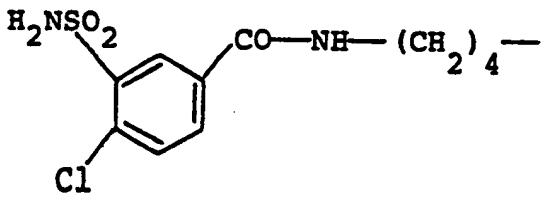
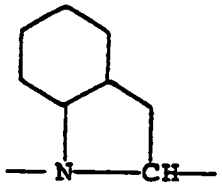
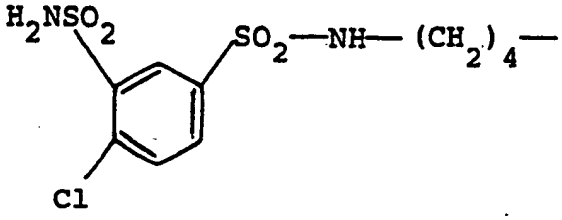
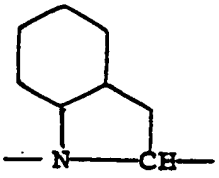
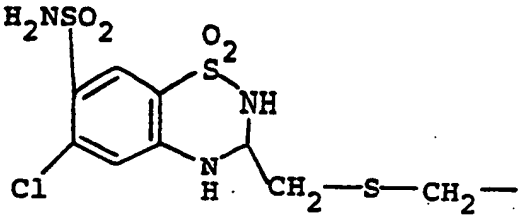
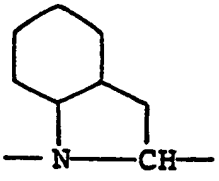
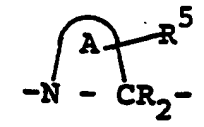
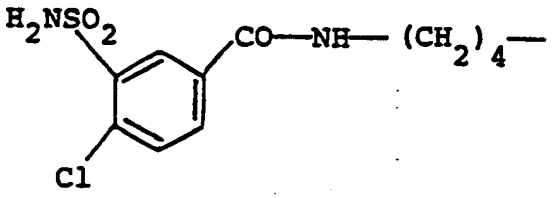
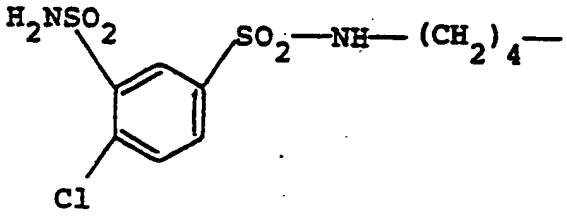
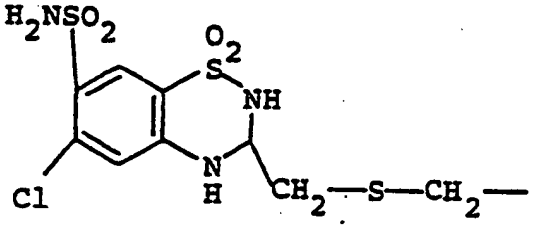
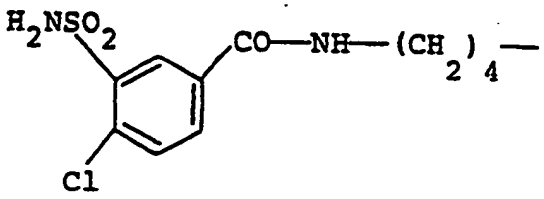
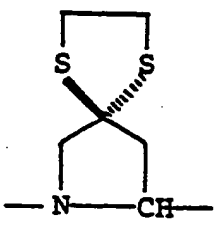
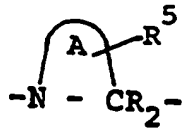
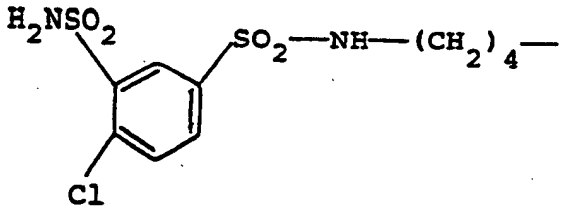
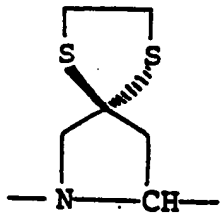
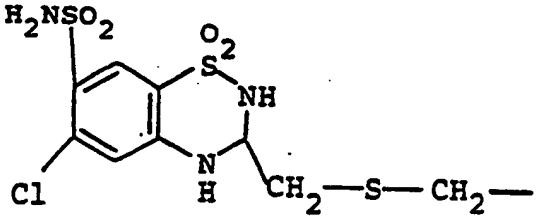
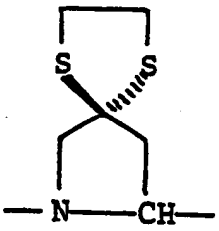
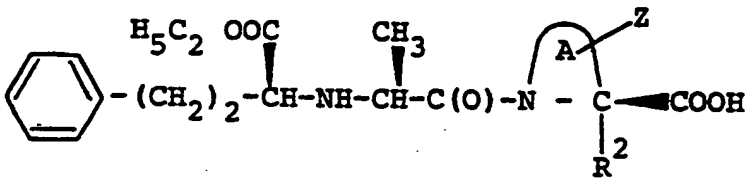
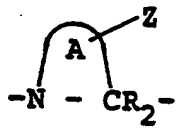
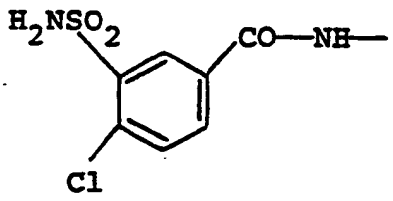
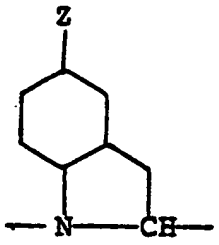
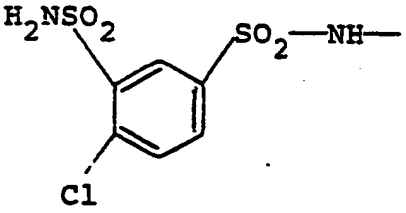
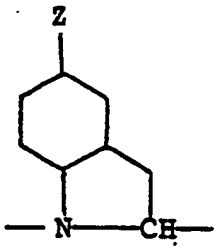
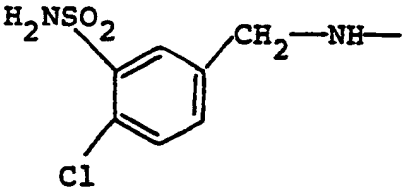
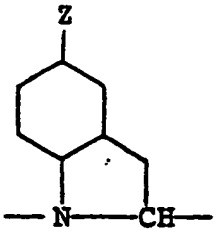
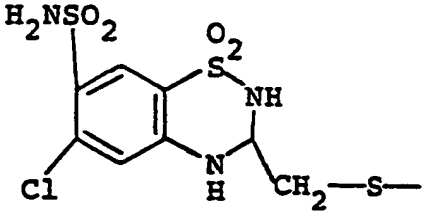
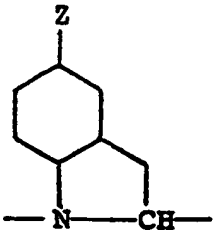
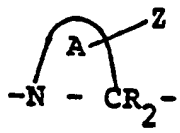
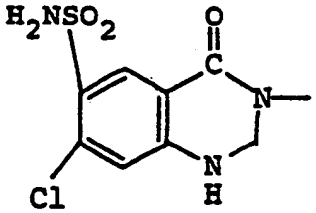
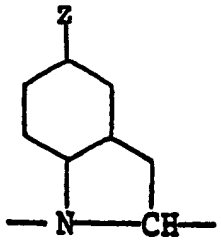
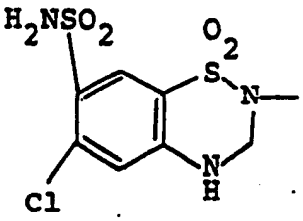
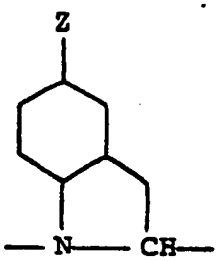
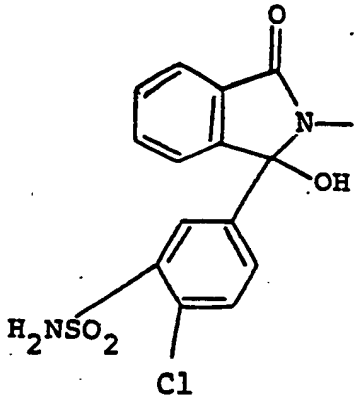
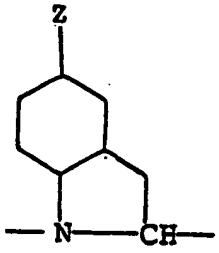
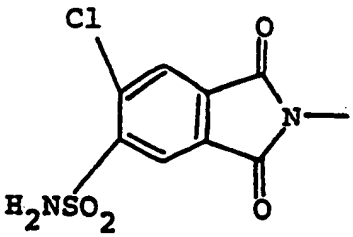
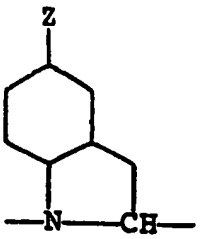
93		
94		
95		

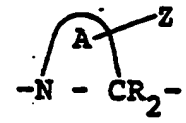
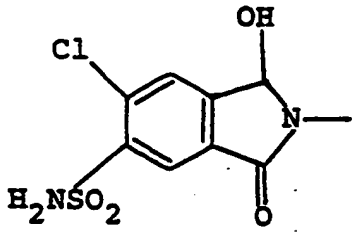
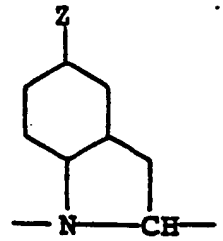
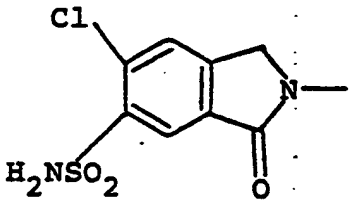
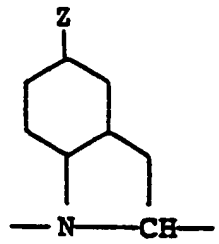
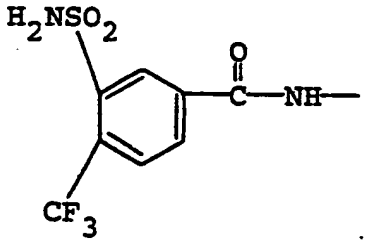
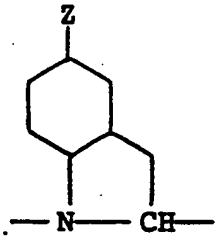
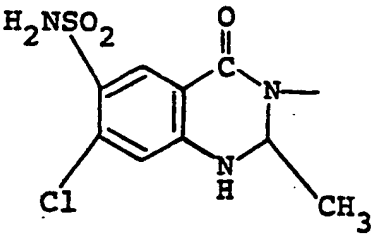
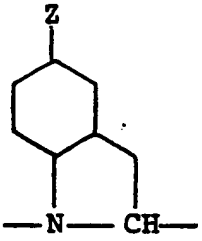
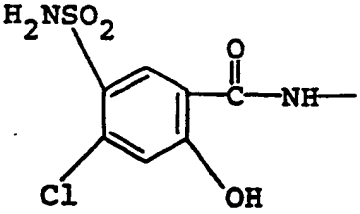
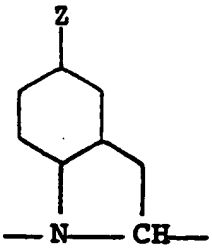
No.	R^3	
96		
97		
98		
99		

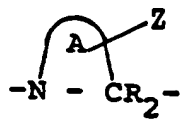
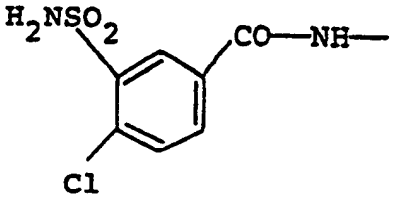
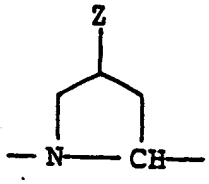
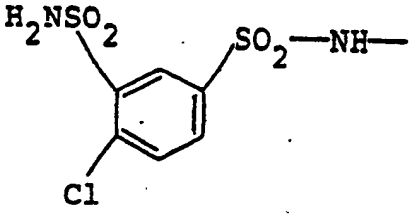
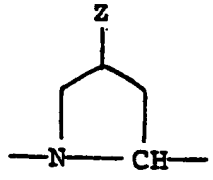
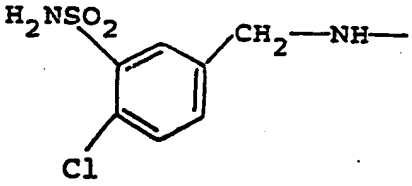
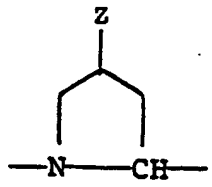
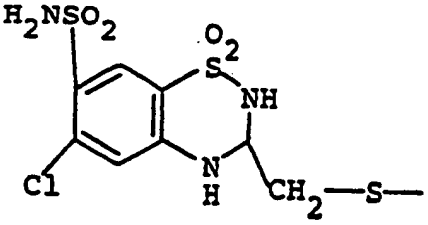
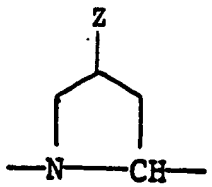
No.	R^3	
100		
101		

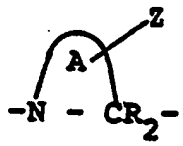
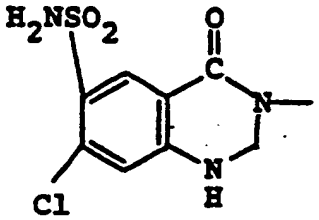
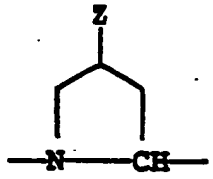
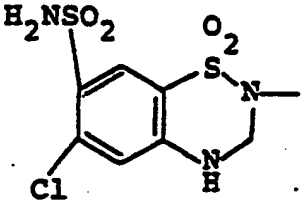
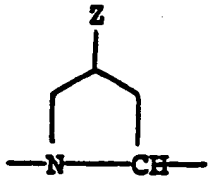
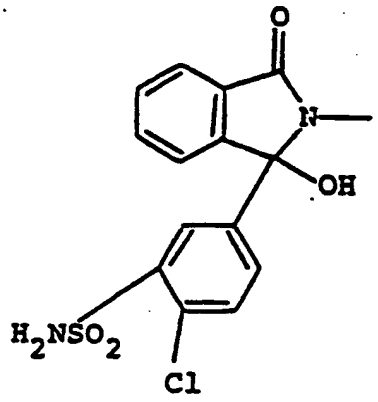
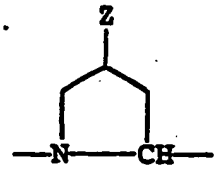
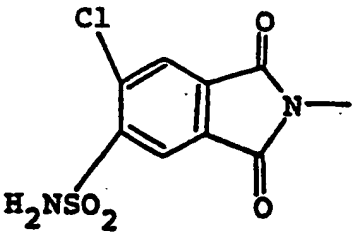
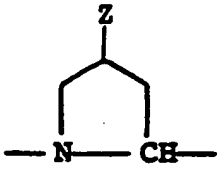


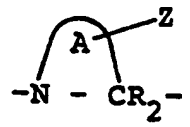
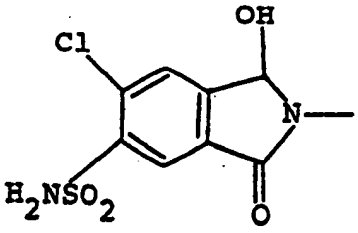
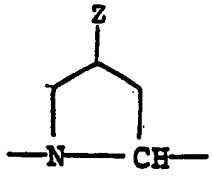
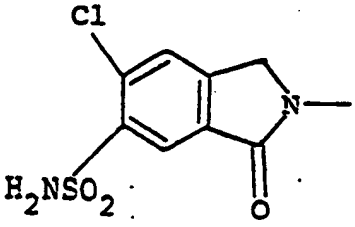
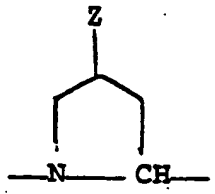
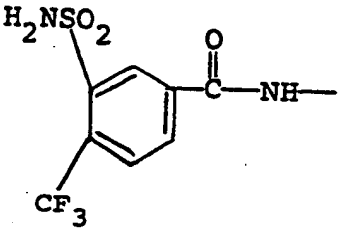
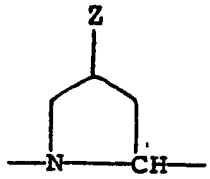
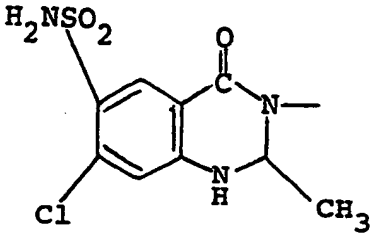
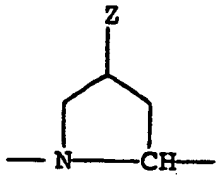
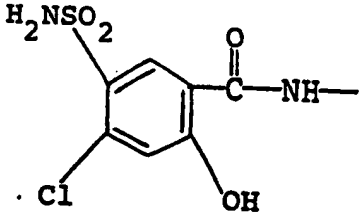
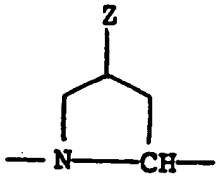
No.	Z	
102		
103		
104		
105		

No.	Z	
106		
107		
108		
109		

No.	Z	
110		
111		
112		
113		
114		

No.	Z	
115		
116		
117		
118		

N.	Z	
119		
120		
121		
122		

No.	Z	
123		
124		
125		
126		
127		

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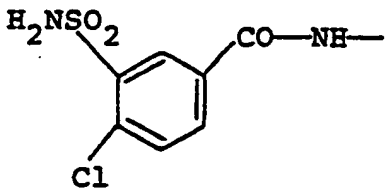
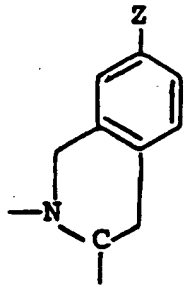
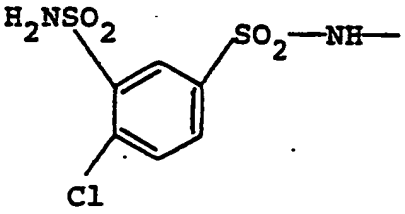
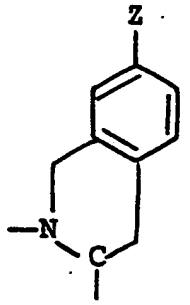
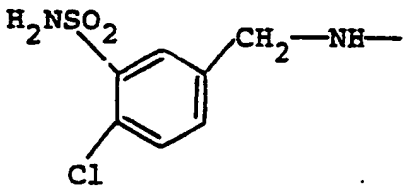
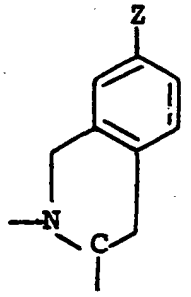
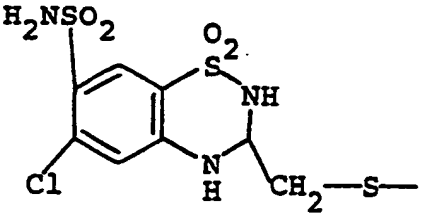
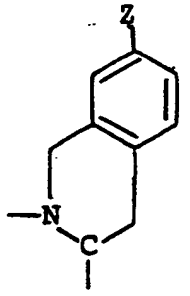
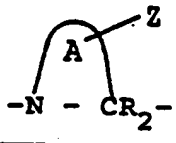
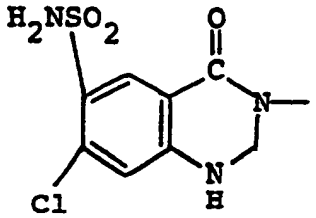
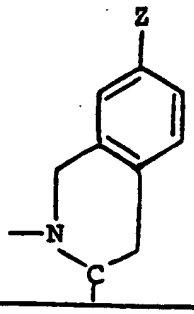
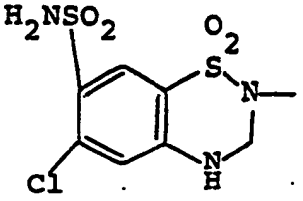
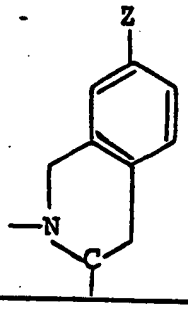
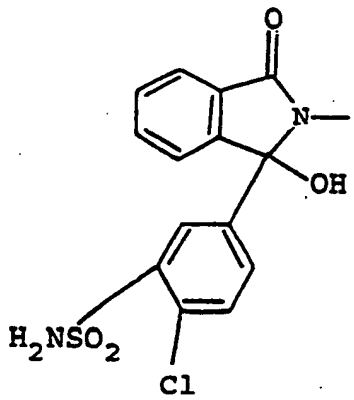
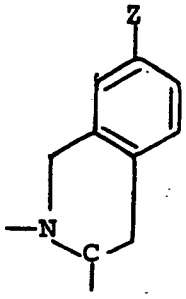
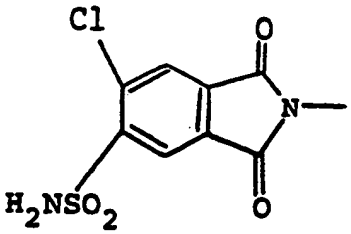
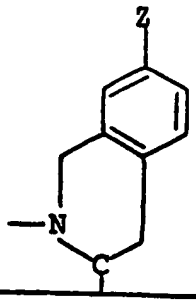
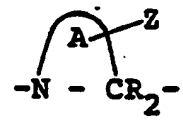
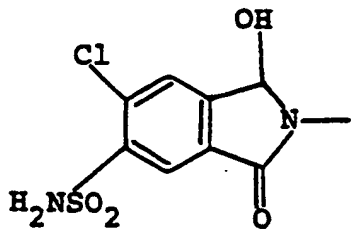
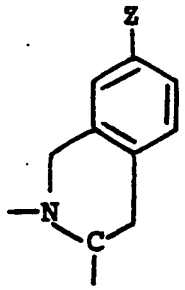
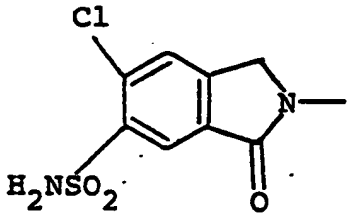
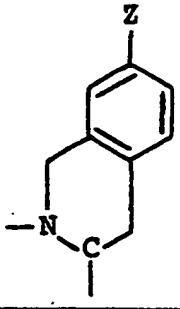
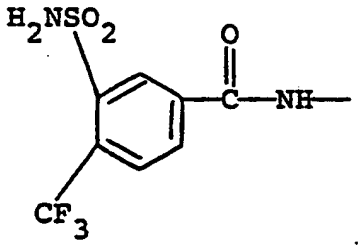
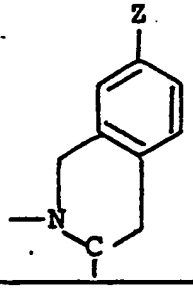
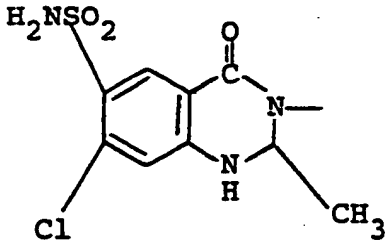
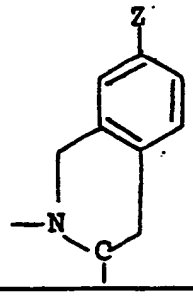
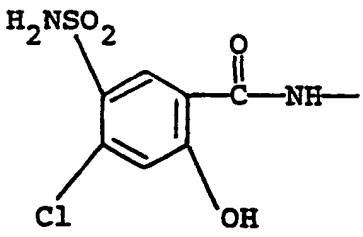
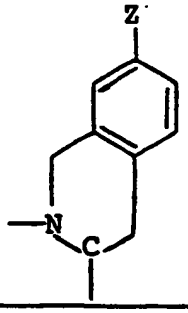
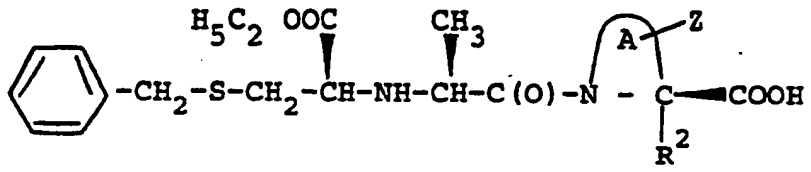
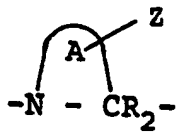
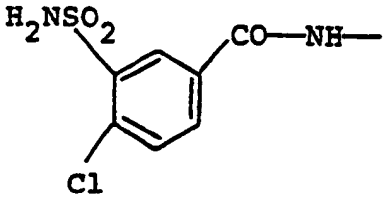
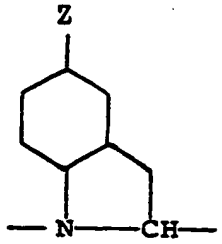
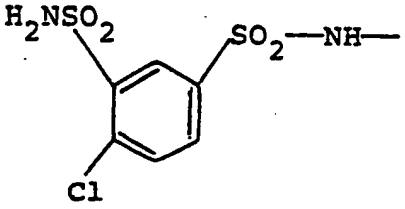
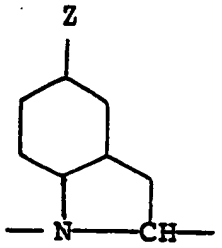
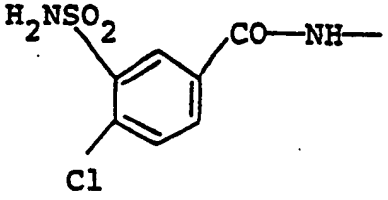
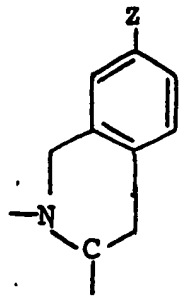
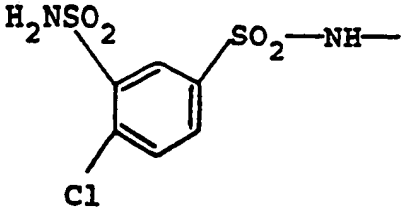
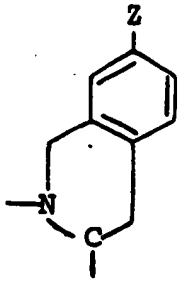
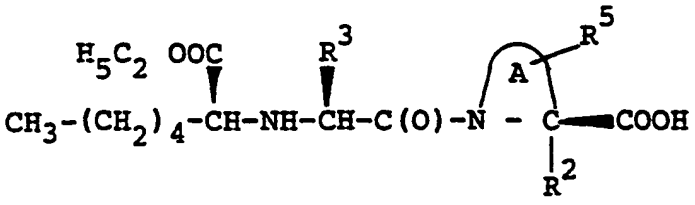
141		
142		
143		
144		

No.	Z	
145		
146		
147		
148		

No.	Z	
149		
150		
151		
152		
153		



No.	Z	
154		
155		
156		
157		



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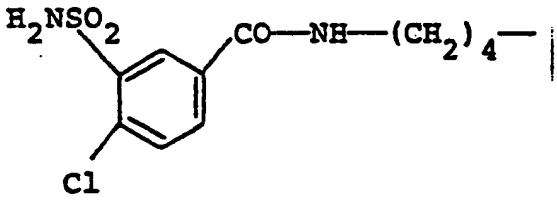
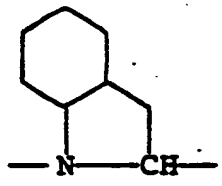
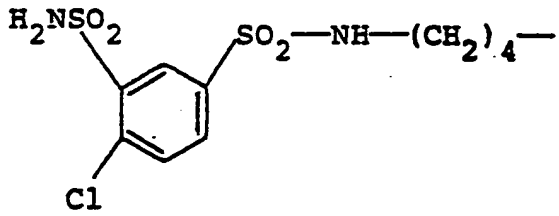
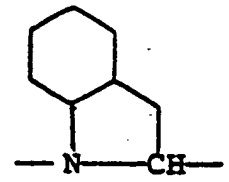
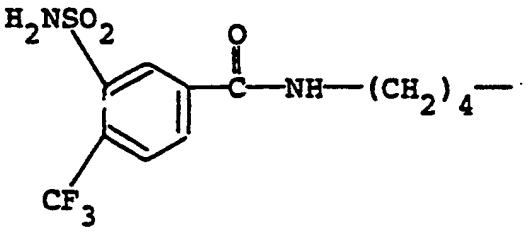
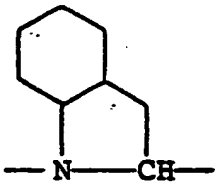
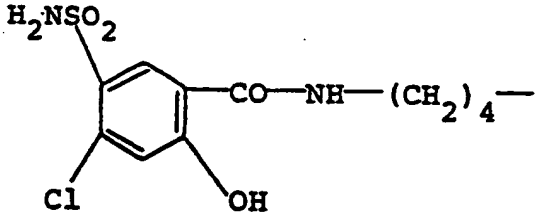
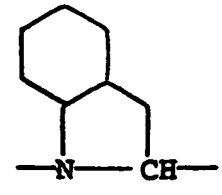
158		
159		
160		
161		

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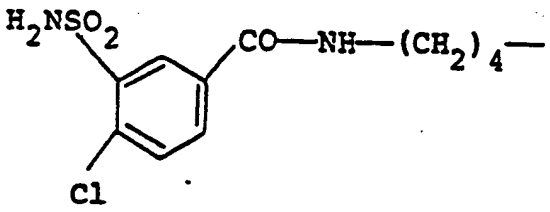
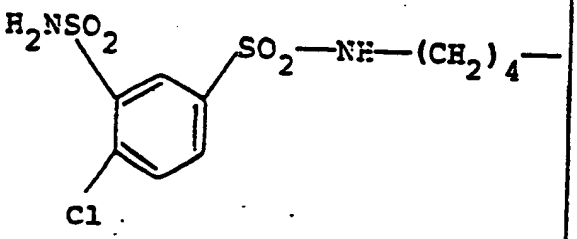
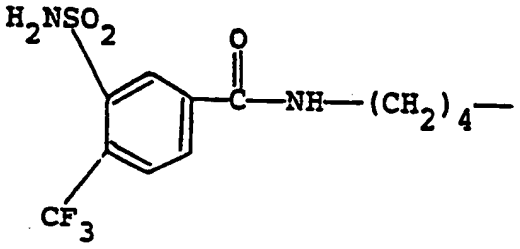
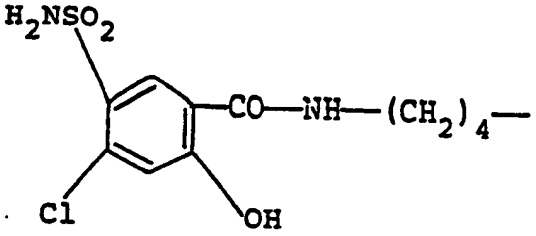
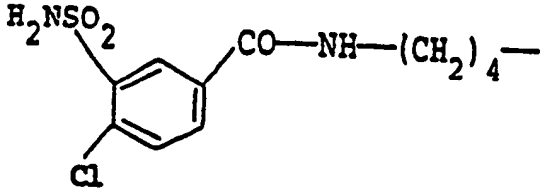
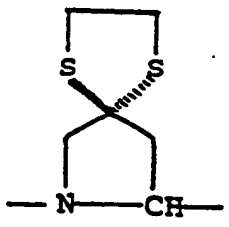
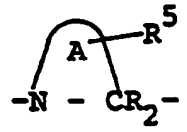
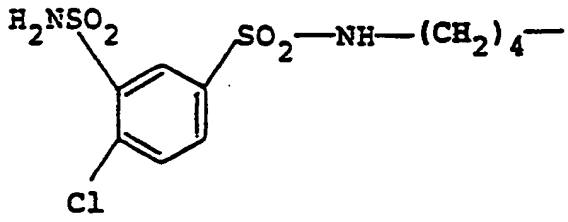
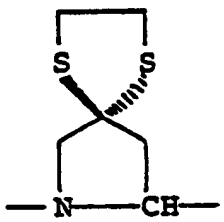
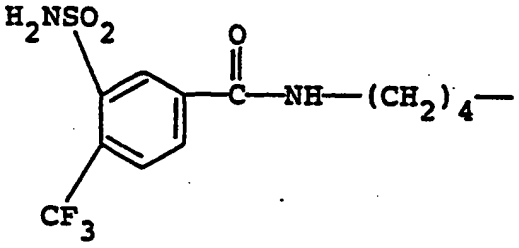
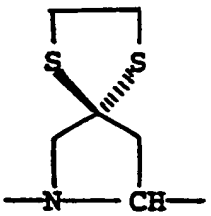
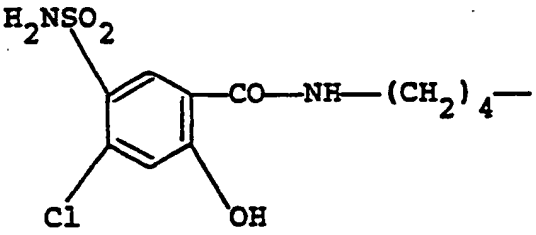
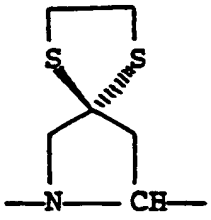
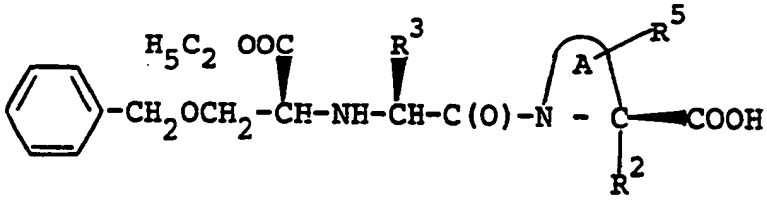
162		
163		
164		
165		
166		

No.	R^3	
167		
168		
169		



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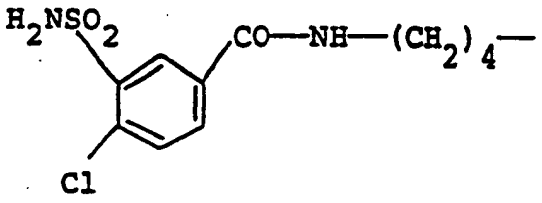
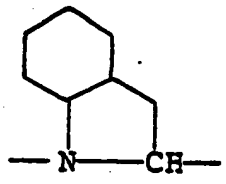
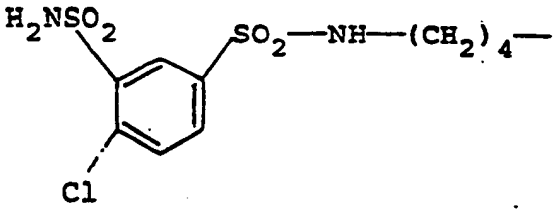
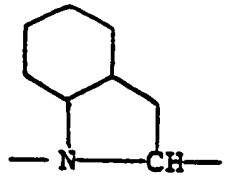
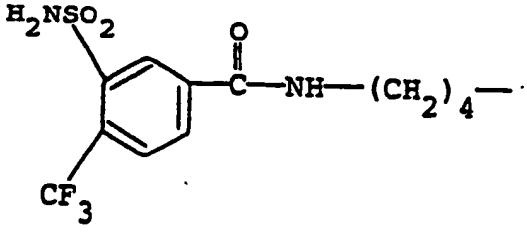
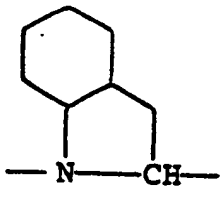
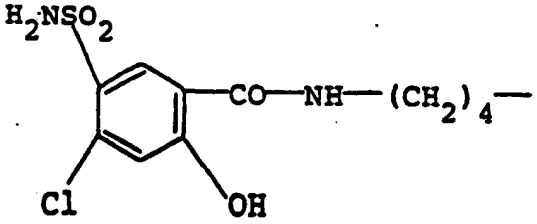
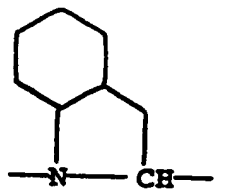
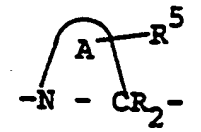
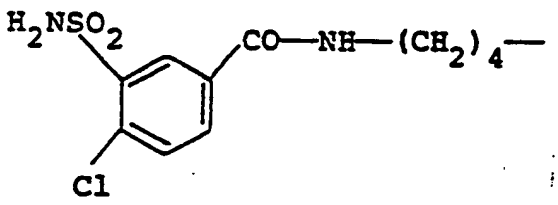
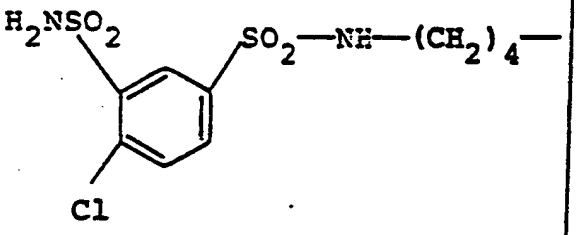
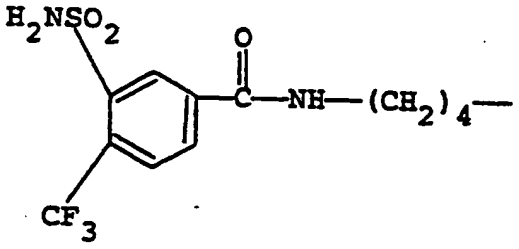
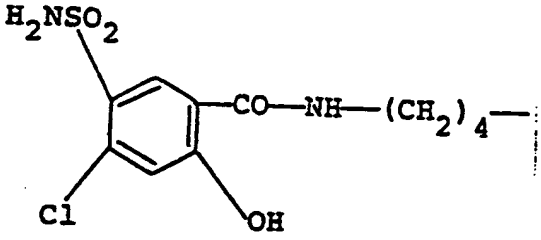
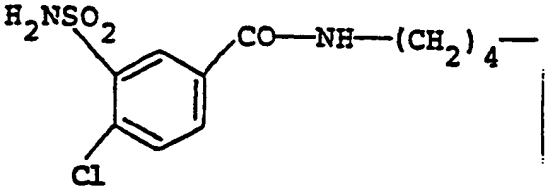
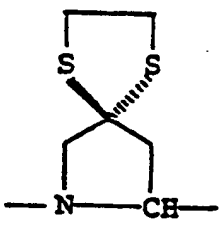
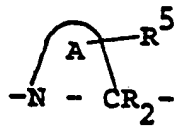
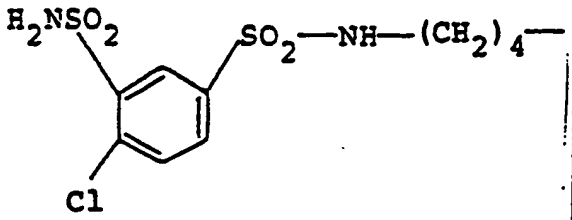
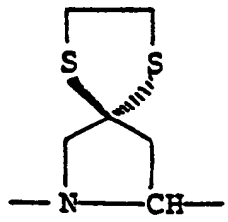
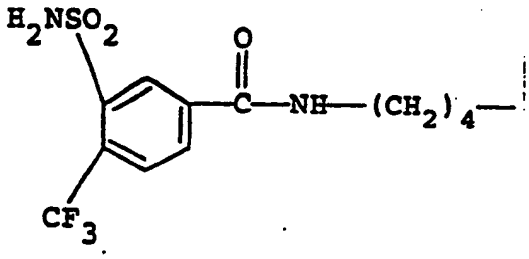
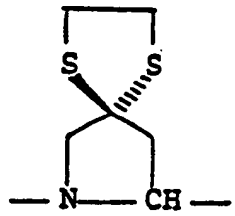
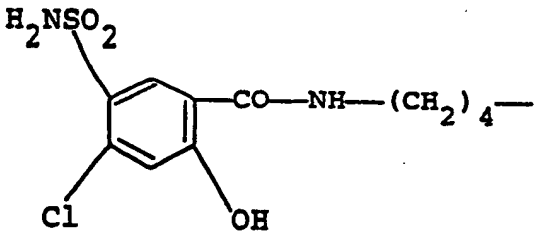
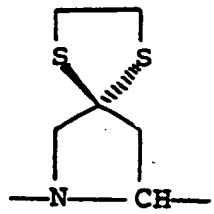
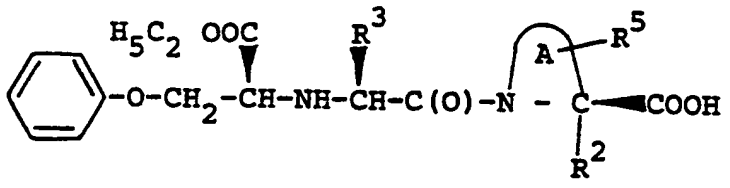
170		
171		
172		
173		

No.	R^3	
174		
175		
176		
177		
178		

No.	R^3	
179		
180		
181		



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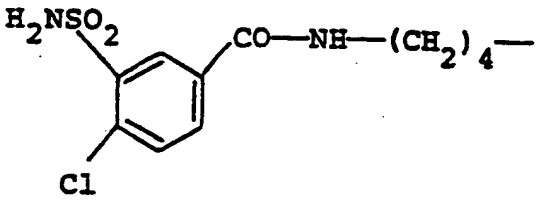
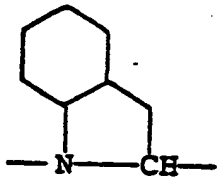
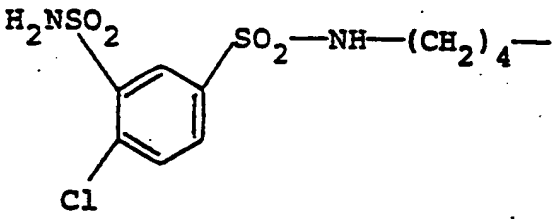
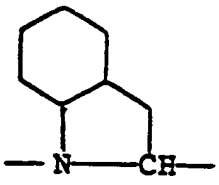
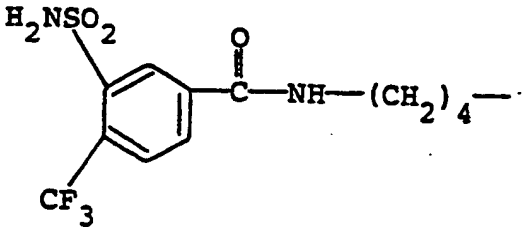
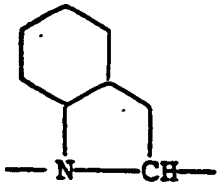
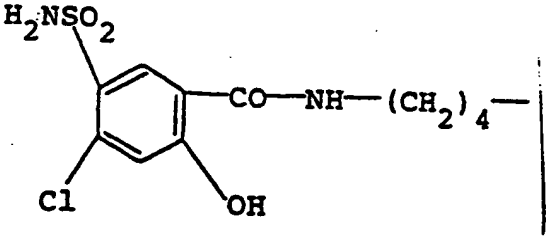
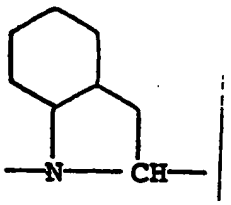
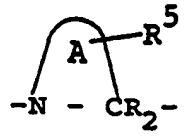
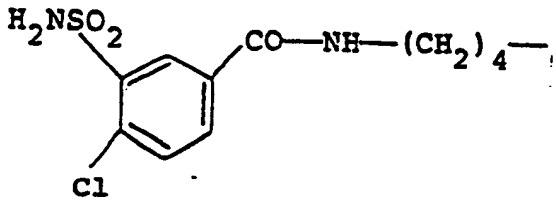
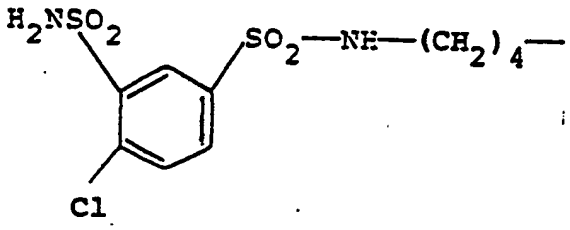
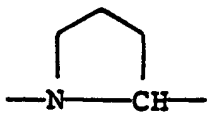
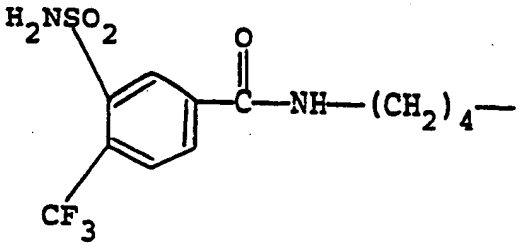
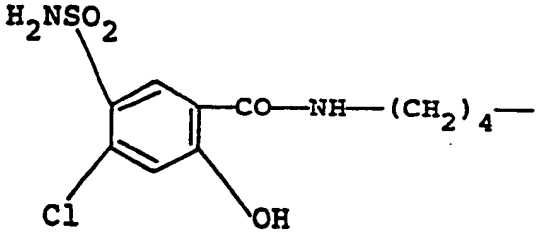
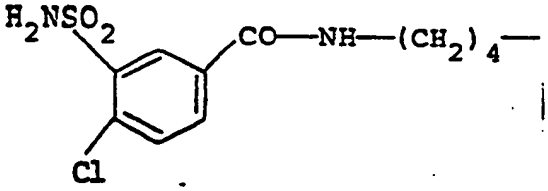
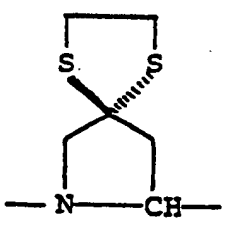
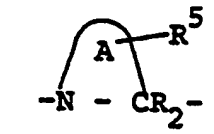
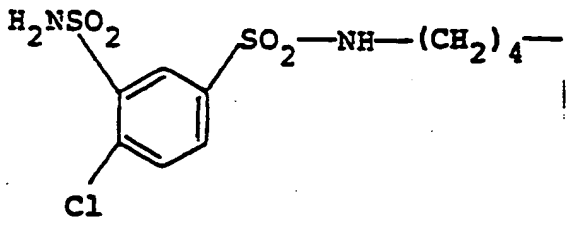
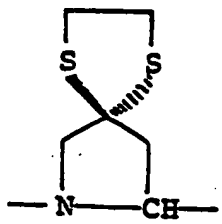
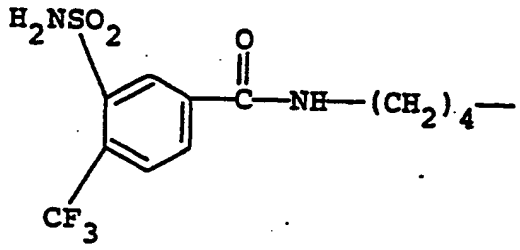
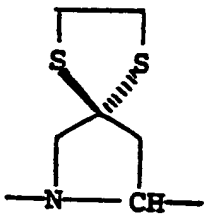
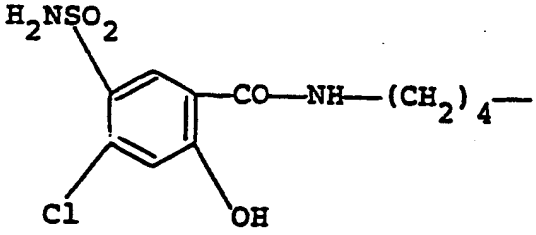
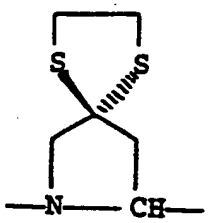
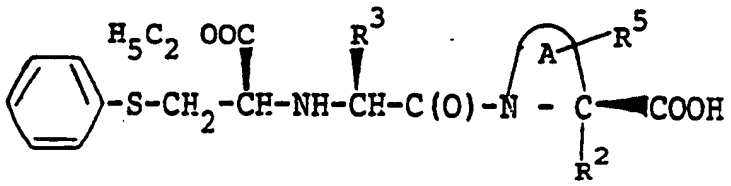
182		
183		
184		
185		

No.	R^3	
186		
187		
188		
189		
190		

No.	R^3	
191		
192		
193		



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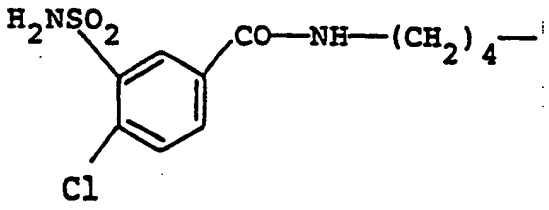
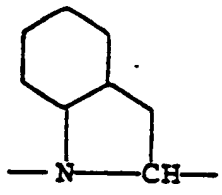
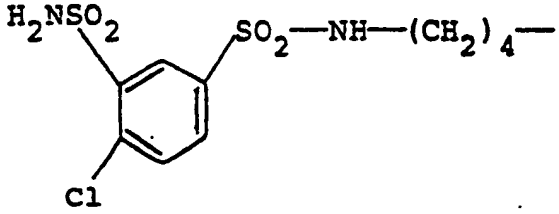
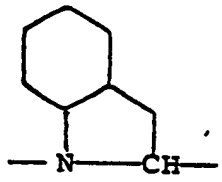
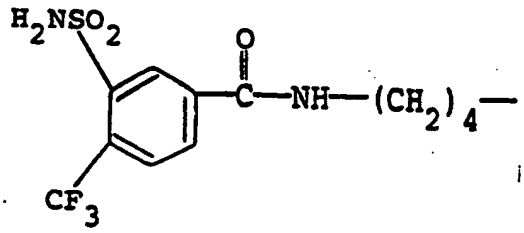
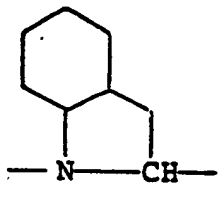
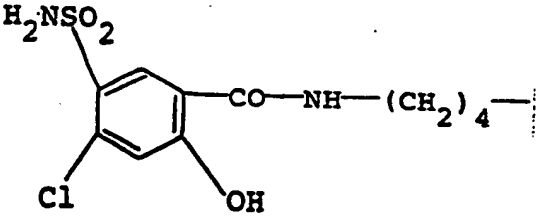
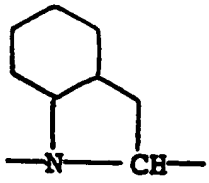
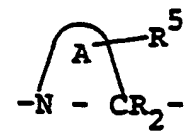
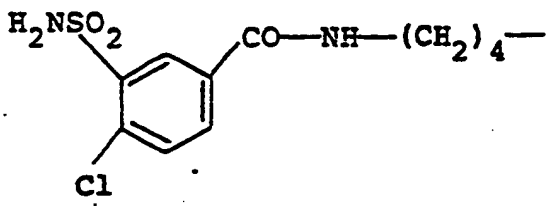
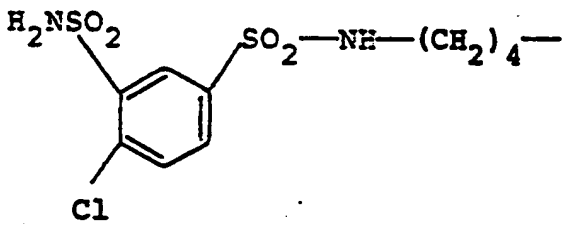
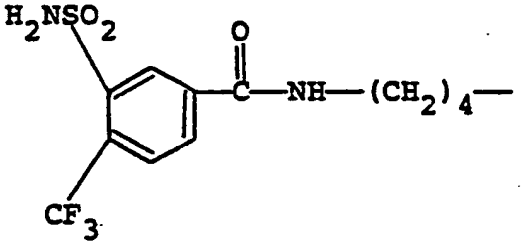
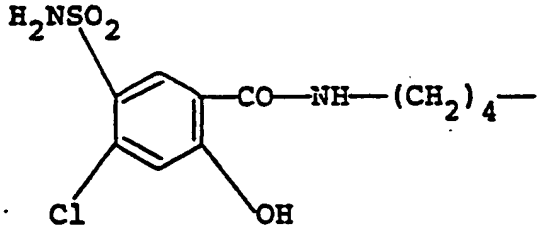
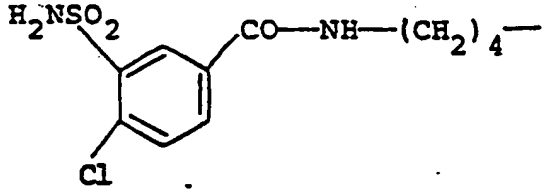
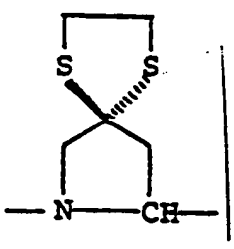
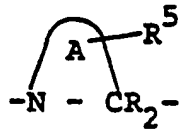
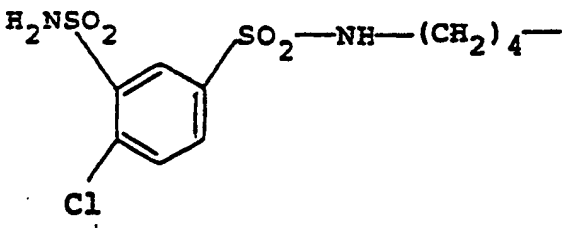
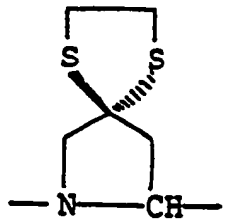
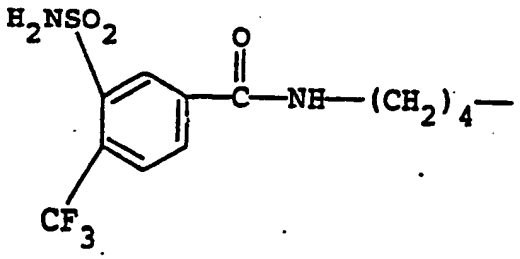
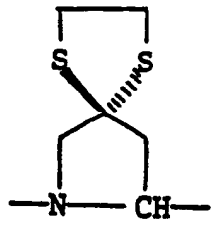
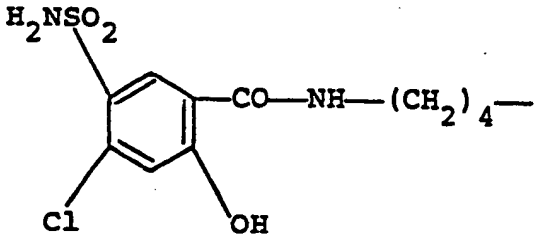
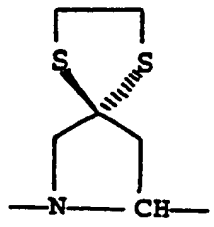
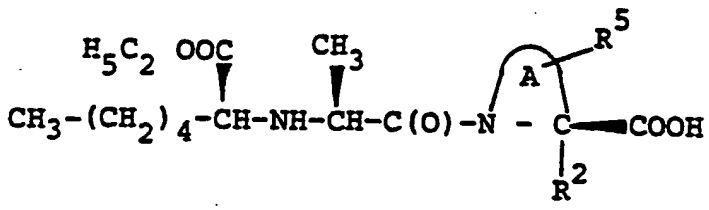
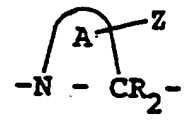
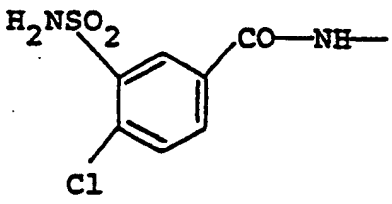
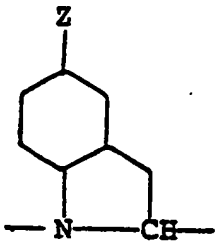
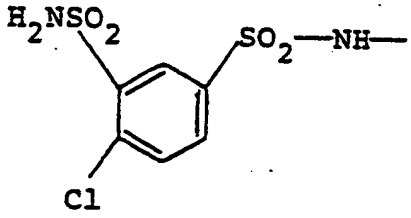
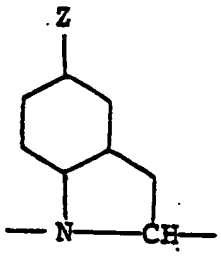
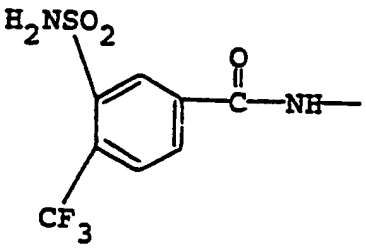
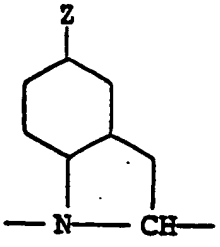
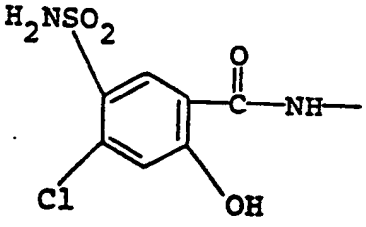
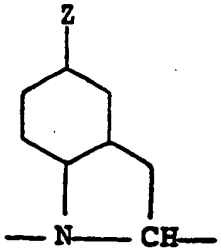
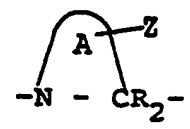
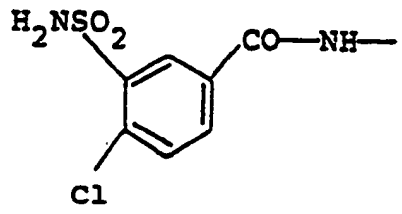
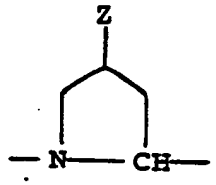
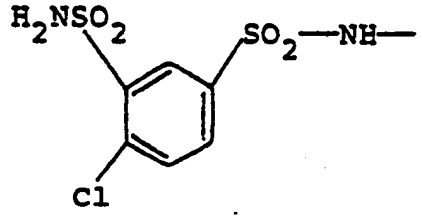
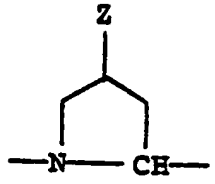
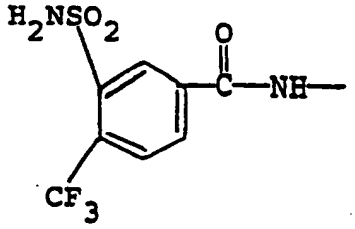
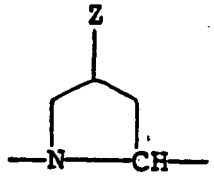
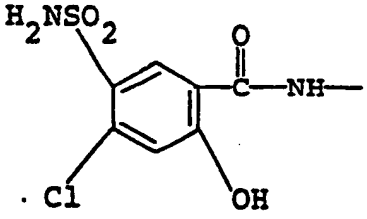
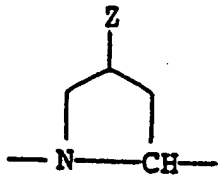
194		
195		
196		
197		

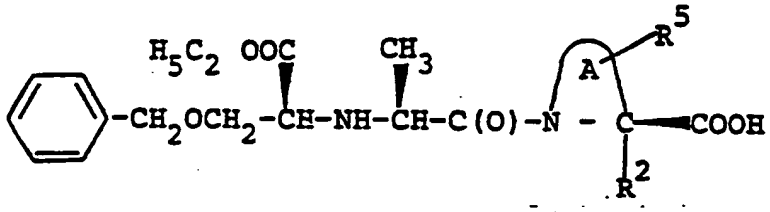
No.	R^3	
198		
199		
200		
201		
202		

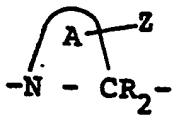
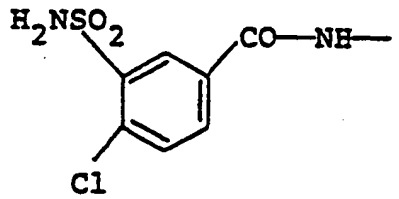
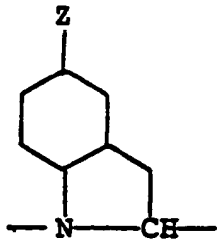
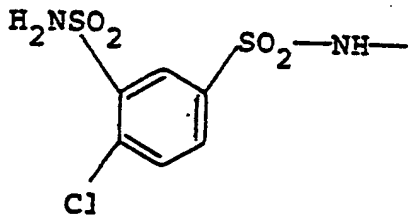
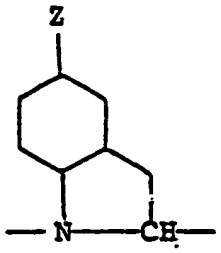
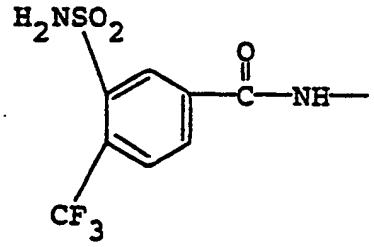
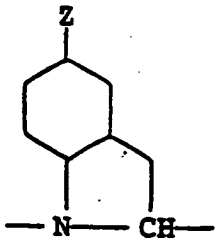
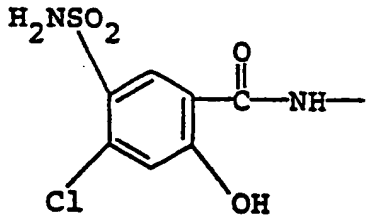
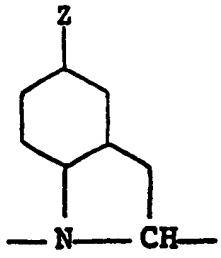
No.	R^3	
203		
204		
205		

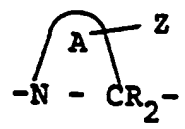
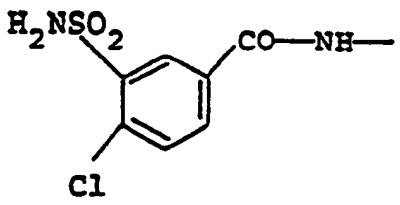
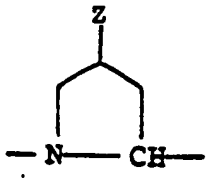
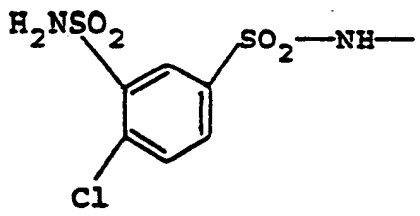
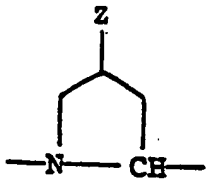
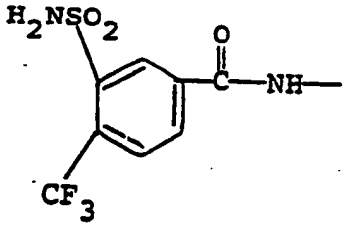
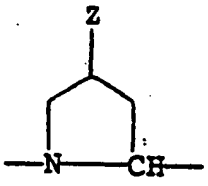
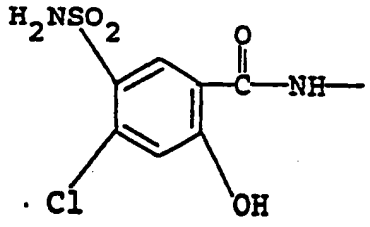
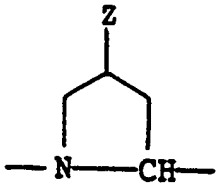


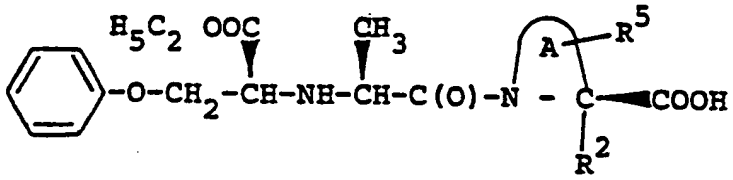
No.	Z	
206		
207		
208		
209		

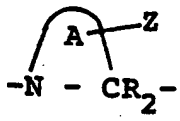
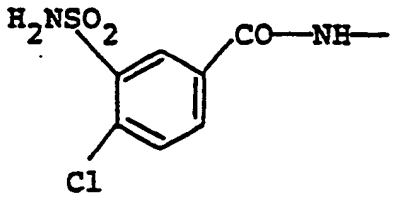
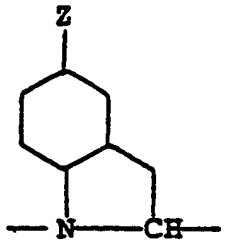
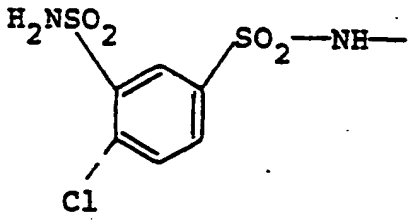
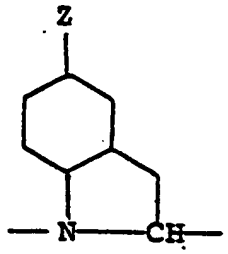
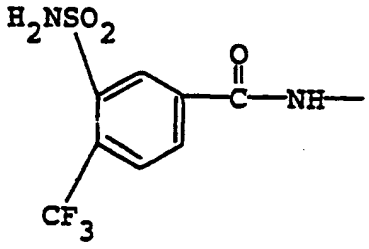
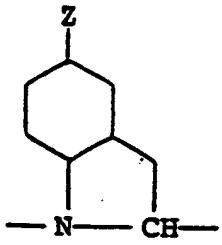
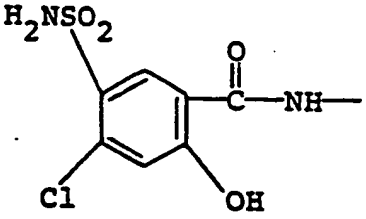
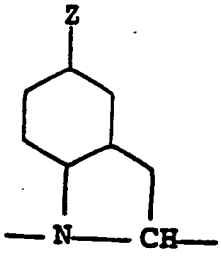
No.	Z	
210		
211		
212		
213		

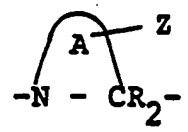
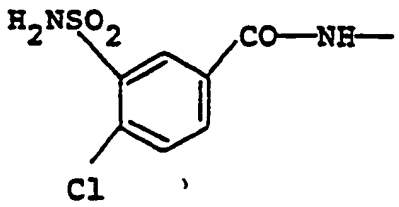
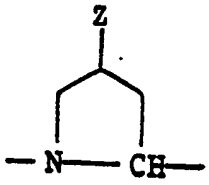
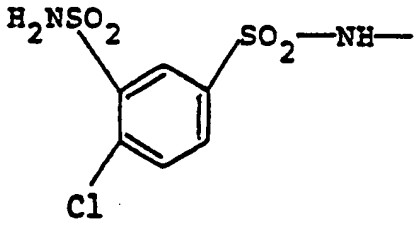
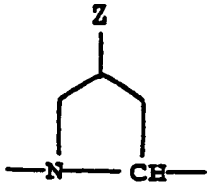
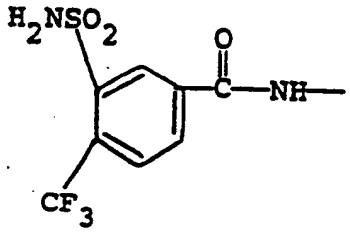
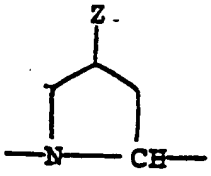
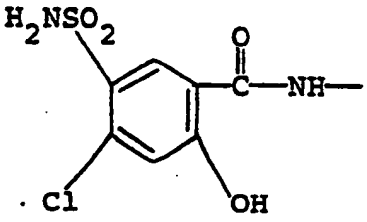
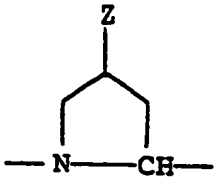


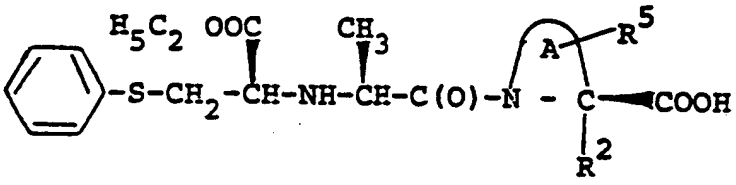
No.	Z	
214		
215		
216		
217		

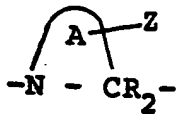
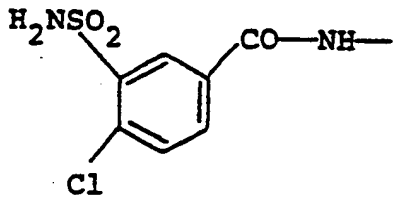
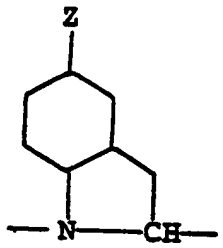
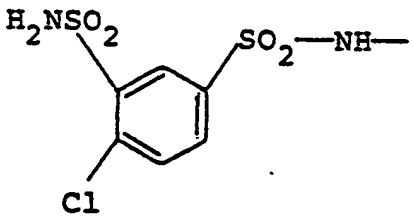
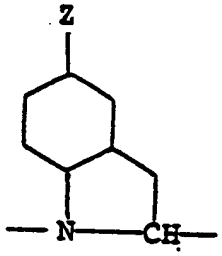
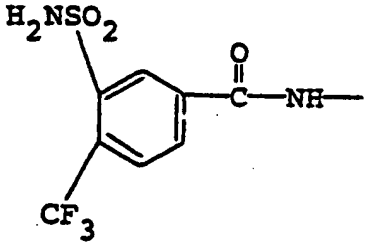
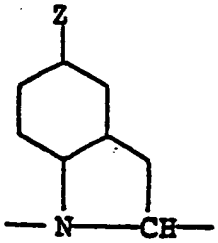
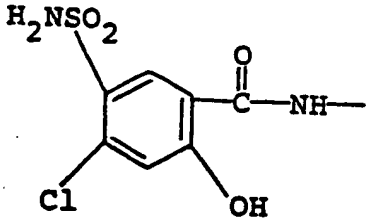
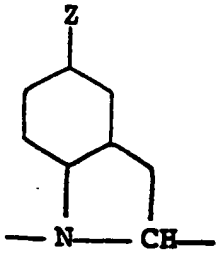
No.	Z	
218		
219		
220		
221		

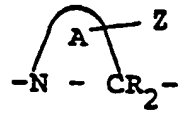
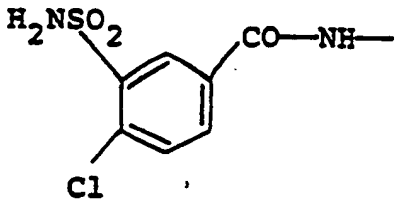
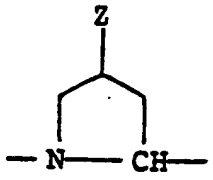
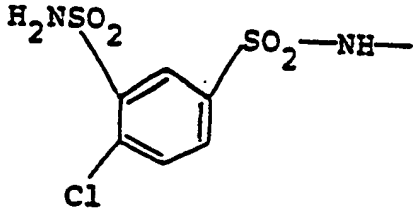
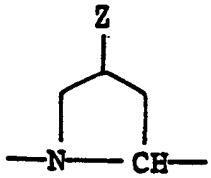
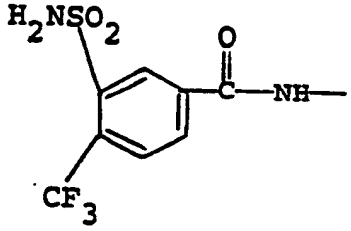
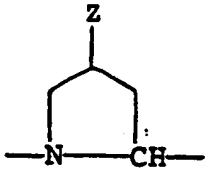
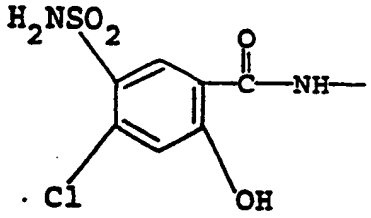
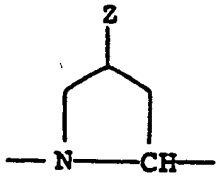


No.	Z	
222		
223		
224		
225		

No.	Z	
226.		
227		
228		
229		



No.	Z	
230		
231		
232		
233		

No.	Z	
234		
235		
236		
237		

Th following examples of formulation describe in detail compositions that are illustrative of the present invention. It will be apparent to those skilled in the art that many modifications, both of materials and methods, may be practiced without departing from the purpose and intent of this disclosure.

In the formulation - examples the active ingredients are as follows:

Active ingredient A:
1-{Nα-[1(S)-ethoxycarbonyl-3-phenylpropyl]-Nε-[(4-chloro-3-sulfamoyl)benzenesulfonyl]-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid.

Active ingredient B:
1-{N-[1(R)-carboxy-2-[S-((3-(6-chloro-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazinyl-1,1-dioxide)methyl))thio]ethyl]]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid.

Active ingredient C:
7-(4-chloro-3-sulfamoylbenzamido)-2-{N-[1(S)-carboethoxy-3-phenylpropyl]-(S)-alanyl}-1,2,3,4-tetrahydroisoquinolin-3(S)-carboxylic acid.

Formulation 1

Capsule	Amount (mg)	
Active ingredient A	250.0	125.0
Lactose	173.0	86.5
Corn Starch	75.0	37.5
Magnesium Stearate	2.0	1.0
	500.0	250.0

Blend the active ingredient, lactose and corn starch until uniform; then blend the magnesium stearate into the resulting powder. Encapsulate the mixture into suitably sized two-piece hard gelatin capsules.

Formulation 2

Tablet	Amount (mg)	
Active ingredient A	250.0	125.0
Lactose	161.0	80.5
Corn Starch	12.0	6.0
Water (per thousand tablets)	120 ml (evaporates)	60 ml (evaporates)
Corn Starch	75.0	37.5
Magnesium Stearate	2.0	1.0
	500.0	250.0

Blend the active ingredient with the lactose until uniform. Blend the smaller quantity of corn starch with the water and add the resulting corn starch paste, then mix until a uniform wet mass is formed. Add the remaining corn starch to the remaining wet mass and mix until uniform granules are obtained. Screen the granules through a suitable milling machine, using a 3/4 inch stainless steel screen. Dry the milled granules in a suitable drying oven until the desired moisture content is obtained. Mill the dried granules through a suitable milling machine using a 16 mesh stainless steel screen. Blend in the magnesium stearate and compress the resulting mixture into tablets of d sired shape, thickness, hardness and disint gration.

Formulation 3

Injectable Solution	mg/ml
Active ingredient A	5.00
Methyl p-hydroxybenzoate	0.80
Propyl p-hydroxybenzoate	0.10
Disodium Edetate	0.10
Citric Acid Monohydrate	0.08
Dextrose	40.0
Water for injection qs. ad.	1.0 ml

Dissolve the p-hydroxybenzoates in a portion of water for injection at 60-70°C and cool the solution to 25-35°C. Charge and dissolve all other excipients and the active ingredient. Bring the solution to final volume, filter it through a sterilizing membrane and fill into sterile containers.

Formulation 4

Capsule	Amount (mg)	
Active ingredient B	250.0	125.0
Lactose	173.0	86.5
Corn Starch	75.0	37.5
Magnesium Stearate	2.0	1.0
	500.0	250.0

Blend the active ingredient, lactose and corn starch until uniform; then blend the magnesium stearate into the resulting powder. Encapsulate the mixture into suitably sized two-piece hard gelatin capsules.

Formulation 5

Tablet	Amount (mg)	
Active ingredient B	250.0	125.0
Lactose	161.0	80.5
Corn Starch	12.0	6.0
Water (per thousand tablets)	120 ml (evaporates)	60 ml (evaporates)
Corn Starch	75.0	37.5
Magnesium Stearate	2.0	1.0
	500.0	250.0

Blend the active ingredient with the lactose until uniform. Blend the smaller quantity of corn starch with the water and add the resulting corn starch paste, then mix until a uniform wet mass is formed. Add the remaining corn starch to the remaining w t mass and mix until uniform granul s are obtained. Scr en th

granul s through a suitable milling machine, using a 3/4 inch stainless steel screen. Dry the milled granules in a suitable drying oven until the desired moisture content is obtained. Mill the dried granules through a suitable milling machine using a 16 mesh stainless steel screen. Blend in the magnesium stearate and compress the resulting mixture into tablets of desired shape, thickness, hardness and disintegration.

Formulation 6

Injectable Solution	mg/ml
Active ingredient B	5.00
Methyl p-hydroxybenzoate	0.80
Propyl p-hydroxybenzoate	0.10
Disodium Edetate	0.10
Citric Acid Monohydrate	0.08
Dextrose	40.0
Water for injection qs. ad.	1.0 ml

Dissolve the p-hydroxybenzoates in a portion of water for injection at 60-70°C and cool the solution to 25-35°C. Charge and dissolve all other excipients and the active ingredient. Bring the solution to final volume, filter it through a sterilizing membrane and fill into sterile containers.

Formulation 7

Capsule	Amount (mg)	
Active ingredient C	250.0	125.0
Lactose	173.0	86.5
Corn Starch	75.0	37.5
Magnesium Stearate	2.0	1.0
	500.0	250.0

Blend the active ingredient, lactose and corn starch until uniform; then blend the magnesium stearate into the resulting powder. Encapsulate the mixture into suitably sized two-piece hard gelatin capsules.

Formulation 8

Tablet	Amount (mg)	
Active ingredient C	250.0	125.0
Lactose	161.0	80.5
Corn Starch	12.0	6.0
Water (per thousand tablets)	120 ml (evaporates)	60 ml (evaporates)
Corn Starch	75.0	37.5
Magnesium Stearate	2.0	1.0
	500.0	250.0

Blend the active ingredient with the lactose until uniform. Blend the smaller quantity of corn starch with the water and add the resulting corn starch paste, then mix until a uniform wet mass is formed. Add the remaining corn starch to the remaining wet mass and mix until uniform granules are obtained. Screen the granules through a suitable milling machine, using a 3/4 inch stainless steel screen. Dry the milled granules in a suitable drying oven until the desired moisture content is obtained. Mill the dried granules through a suitabl milling machine using a 16 mesh stainless steel screen. Blend in the magnesium stearate and compress the resulting mixture into tablets of desir d shap , thickness, hardness and disintegration.

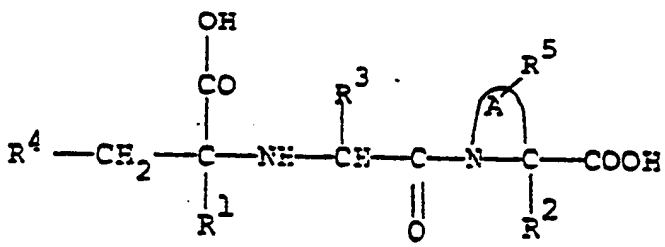
Formulation 9

Injectable Solution	mg/ml
Active ingredient C	5.00
Methyl p-hydroxybenzoate	0.80
Propyl p-hydroxybenzoate	0.10
Disodium Edetate	0.10
Citric Acid Monohydrate	0.08
Dextrose	40.0
Water for injection qs. ad.	1.0 ml

Dissolve the p-hydroxybenzoates in a portion of water for injection at 60-70°C and cool the solution to 25-35°C. Charge and dissolve all other excipients and the active ingredient. Bring the solution to final volume, filter it through a sterilizing membrane and fill into sterile containers.

We claim:

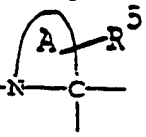
1) A compound of the formula

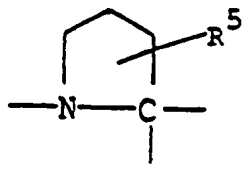


(I),

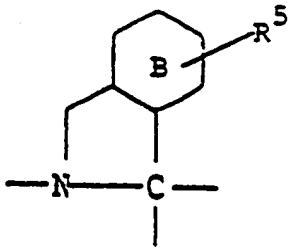
the pharmaceutically acceptable esters thereof and the pharmaceutically acceptable salts of the foregoing, wherein

R^1 and R^2 independently are hydrogen or lower alkyl;

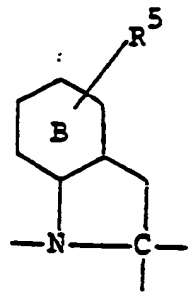
the group  is one of the structures II to VIII



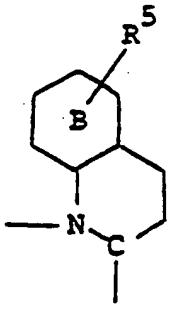
II



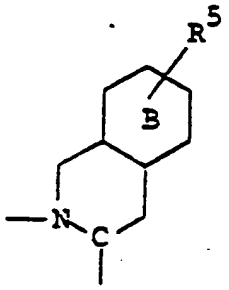
III



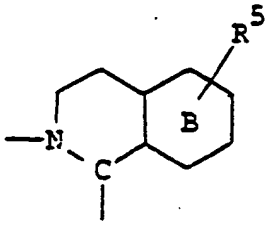
IV



V

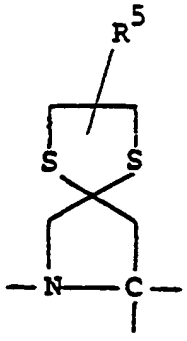


VI



VII

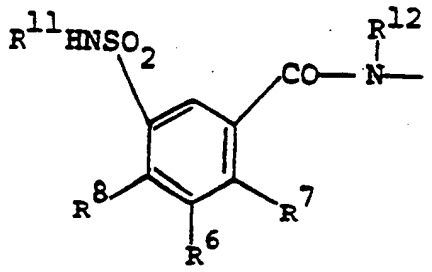
(wherein B is a saturated or aromatic ring) or



VIII

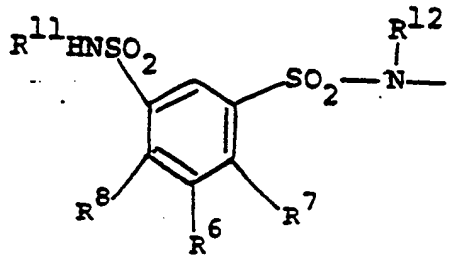
one of R^3, R^4 and R^5 is a group $Z-(CH_2)_{0-6}-$, wherein Z has one of the following values Z^1 to Z^{10}:

Z^1:



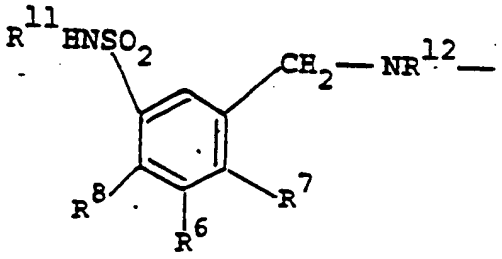
IX

Z^2:



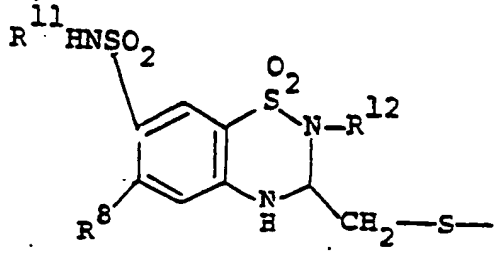
X

Z^3:



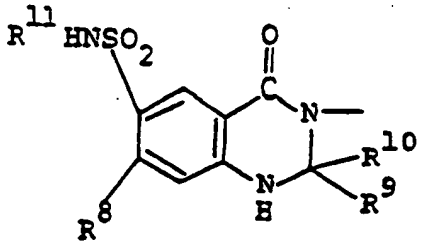
XI

Z^4:



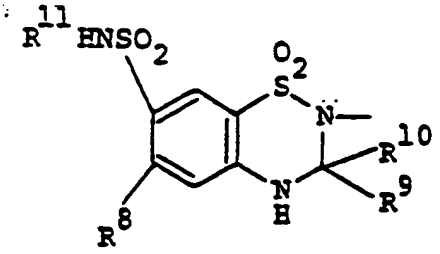
XII

Z^5:



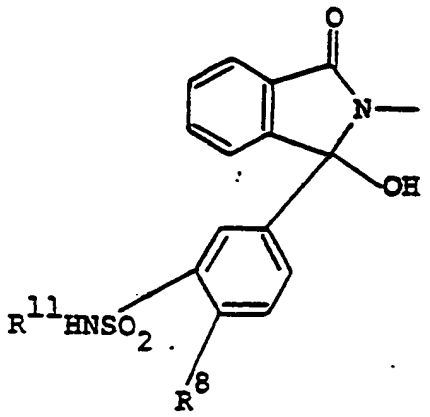
XIII

Z^6:



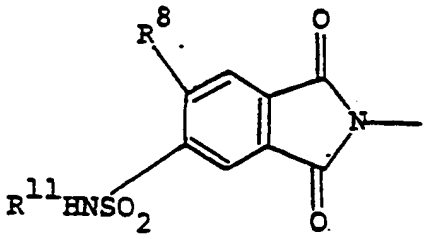
XIV

Z^7:



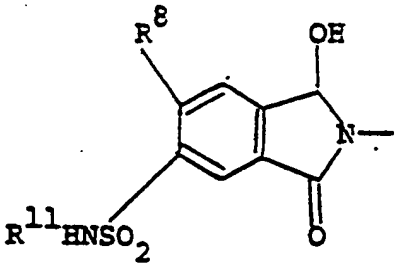
XV

Z^8:



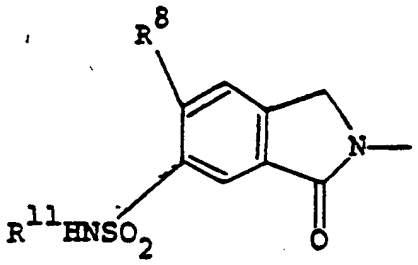
XVI

Z^9:



XVII

Z^{10}:



XVIII

wherein R^8 is Cl or CF_3;

R^6 is hydrogen or halogen;

R^7 is hydrogen, halogen, carboxy, hydroxy or amino;

R^9 and R^{10} are independently hydrogen, lower alkyl or halo-lower alkyl and R^9 can also be phenyl or phenyl lower alkyl;

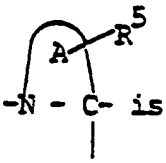
R^{11} is hydrogen or lower alkyl;

R^{12} is hydrogen, lower alkyl or phenyl lower alkyl;

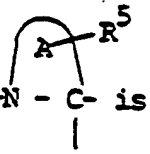
whereby when R^3 is the group $Z-(CH_2)_{0-6}-$, then

R^3 is $Z^1-(CH_2)_{1-6}-$, $Z^2-(CH_2)_{1-6}-$, $Z^3-(CH_2)_{1-6}-$, Z^4-CH_2-, $Z^5-(CH_2)_{1-6}-$, $Z^6-(CH_2)_{1-6}-$, $Z^7-(CH_2)_{1-6}-$, $Z^8-(CH_2)_{1-6}-$, $Z^9-(CH_2)_{1-6}-$, or $Z^{10}-(CH_2)_{1-6}-$,

R^4 is lower alkyl, benzyl, benzyloxy, benzylthio, phenoxy, or phenylthio,

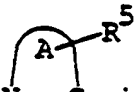
R^5 is hydrogen; and the group  is one of the structures II to VIII;

and when R^4 is the group $Z-(CH_2)_{0-6}-$, then
R^4 is $Z^1-(CH_2)_{0-6}-$, $Z^2-(CH_2)_{0-6}-$, $Z^3-(CH_2)_{0-6}-$, $Z^4-(CH_2)_{0-6}-$, $Z^5-(CH_2)_{0-6}-$, $Z^6-(CH_2)_{0-6}-$, $Z^7-(CH_2)_{0-6}-$, $Z^8-(CH_2)_{0-6}-$, $Z^9-(CH_2)_{0-6}-$ or $Z^{10}-(CH_2)_{0-6}-$ and
R^3 is hydrogen, lower alkyl or amino lower alkyl and

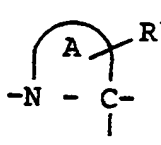


R^5 is hydrogen; and the group $-N-C-$ is one of the structures II to VIII;

and when R^5 is the group $Z-(CH_2)_{0-6}-$, then R^5 is Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, Z^9 or Z^{10},
R^3 is hydrogen, lower alkyl or amino lower alkyl and
R^4 is lower alkyl, benzyl, benzyloxy, benzylthio, phenoxy or phenylthio; and



the group $-N-C-$ is one of the structures II to VII,
preferably being in the form of the free di-carbonic acid or in the form of its aklyl ester, the alkyl group containing 1 to 6 carbon atoms, especially in the form of its monoester wherein the carboxy group attached to the group



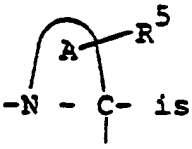
$-N-C-$ is in the free form,

preferably all former compounds being the stereoisomer in which the absolute configurations at each of the three carbon atoms bonded to both a nitrogen and a carbonyl group corresponds most closely to the absolute configuration of L-aminoacids.

2) A compound according to claim 1, wherein R^4 is a group $Z-(CH_2)_{0-6}-$ as defined in claim 1, wherein Z preferably is Z^1, Z^2, Z^3, Z^5, Z^7, Z^8, Z^9 or Z^{10};

R^4 preferably being $Z^1-(CH_2)_2$ or $_3-$, $Z^2-(CH_2)_2$ or $_3-$, $Z^3-(CH_2)_2$ or $_3-$, $Z^5-(CH_2)_2$ or $_3-$, $Z^7-(CH_2)_2$ or $_3-$, $Z^8-(CH_2)_2$ or $_3-$, $Z^9-(CH_2)_2$ or $_3-$ or $Z^{10}-(CH_2)_2$ or $_3-$,

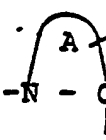
and wherein preferably the group



$-N-C-$ is the group of formula II, IV (wherein B is a saturated ring) or VIII, preferably R^5 being hydrogen.

3) A compound according to claim 1 or 2, wherein R^1 and R^2 are hydrogen, and/or when Z is of the formula IX, X or XI R^6 is hydrogen and R^7 is hydrogen or hydroxy, and/or when Z is of the formula XIII or XIV R^9 and R^{10} are independently hydrogen or methyl, and/or R^8 in the definition of the moiety Z is chloro, and/or R^3 is methyl.

4) A compound according to claim 1 or 2, wherein R^1 and R^2 are hydrogen, the group



-N - C- is the group of formula IV, wherein B is a saturated ring and R^5 is hydrogen, R^4 is Z^1-$(CH_2)_3$- or Z^2-$(CH_2)_3$-, wherein R^6 is hydrogen, R^7 is hydrogen or hydroxy, and R^8 is chloro; and R^3 is methyl, preferably being

1-{N-[1(S)-ethoxycaronyl-5-(4-chloro-3-sulfamoyl)-benzenesulfonaminopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid,

1-{N-[1(S)-ethoxycarbonyl-5-(4-chloro-3-sulfamoyl)-benzamidopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid, or

1-{N-[1(S)-ethoxycarbonyl-5-(4-chloro-2-hydroxy-5-sulfamoyl)-benzamidopentyl]-(S)-alanyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid,

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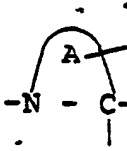
1-{N-[1 (S)-CARBOXY-5-[[(4-CHLORO-2-HYDROXY-5-SULFAMOYL PHENYL) CARBONYL]AMINO]PENTYL]-(S)-ALANYL}-CIS,SYN-OCTAHYDRO-1H-INDOLE-2(S)-CARBOXYLIC ACID,

1-{N-[1(S)-CARBOXY-5-[[(4-CHLORO-3-(N-METHYL SULFAMOYL) PHENYL] CARBONYL]AMINO]PENTYL]-(S)-ALANYL}-CIS,SYN-OCTAHYDRO-1H-INDOLE-2(S)-CARBOXYLIC ACID,

1-{N-[1(S)-CARBOXY-5-[[(4-CHLORO-3-SULFAMOYL PHENYL) CARBONYL]AMINO]PENTYL]-(S)-ALANYL}-CIS,SYN-OCTAHYDRO-1H-INDOLE-2(S)-CARBOXYLIC ACID,

in th fr form or in the form of its ester, preferably in the form of its mono-or-di-ethyl ester.

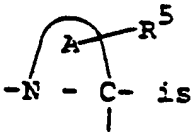
5) A compound according to claim 1, wherein R^3 is a group $Z-(CH_2)_{0-6}-$ as defined in claim 1, preferably $Z^1-(CH_2)_4-$, $Z^2-(CH_2)_4-$, $Z^3-(CH_2)_4-$, Z^4-CH_2-, $Z^5-(CH_2)_4-$, $Z^6-(CH_2)_4-$, $Z^7-(CH_2)_4$, $Z^8-(CH_2)_4-$, $Z^9-(CH_2)_4-$ or $Z^{10}-(CH_2)_4-$, and wherein the group



$-N-C-$ is preferably the group of formula II, IV (wherein B is a saturated ring) or VIII.

6) A compound according to claim 5, wherein R^1 and R^2 are hydrogen, and/or Z is of the formula IX, X or XI, R^6 is hydrogen and R^7 is hydrogen or hydroxy, and/or when Z is of the formula XIII or XIV R^9 and R^{10} are independently hydrogen or methyl, and/or R^8 in the definition of the moiety Z is chloro, and/or R^4 is benzyl or ethyl.

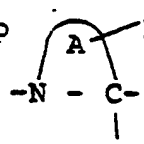
7) A compound according to claim 5, wherein R^1 and R^2 are hydrogen, the group

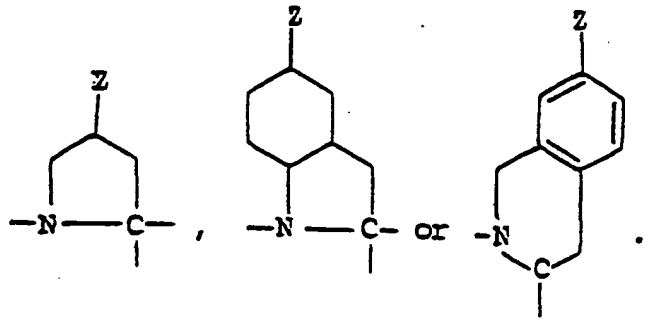


$-N-C-$ is the group of formula IV, wherein B is a saturated ring and R^5 is hydrogen, R^3 is $Z^1-(CH_2)_4-$ or $Z^2-(CH_2)_4-$, wherein R^6 and R^7 are hydrogen, and R^8 is chloro, and R^4 is benzyl, preferably being

1-{Nα-[1(S)-ethoxycarbonyl-3-phenylpropyl]-Nε-[(4-chloro-3-sulfamoyl)benzenesulfonyl]-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid or 1-{Nα-[1(S)-ethoxycarbonyl-3-phenylpropyl]-Nε-[(4-chloro-3-sulfamoyl)benzoyl-(S)-lysyl}-cis,syn-octahydro-1H-indole-2(S)-carboxylic acid

in the free form or in the form of its ester, preferably in the form of its mono-or-di-ethyl ester.

8) A compound according to claim 1, wherein R^5 is a group $Z-(CH_2)_{0-6}-$ as defined in claim 1, preferably being Z^1, Z^2, Z^3, Z^5, Z^7, Z^8, Z^9 or Z^{10}; wherein the group  is preferably the group of formula II, VI (wherein B is an aromatic ring), or IV (wherein B is a saturated ring), preferably



9) A compound according to claim 8, wherein R^1 and R^2 are hydrogen, and/or when Z is of th formula IX, X or XI R^6 is hydrogen and R^7 is hydrogen or hydroxy, and/or when Z is of the formula XIII or XIV R^9 and R^{10} are

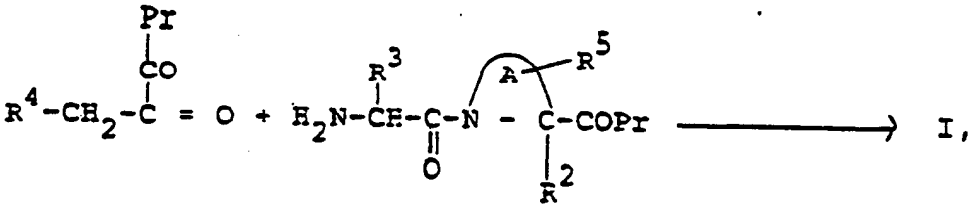
independently hydrogen or methyl, and/or R^8 in the definition of the moiety Z is chloro, and/or R^3 is methyl and/or R^4 is benzyl or ethyl,

the compound preferably being

7-(4-chloro-3-sulfamoylbenzamido)-2-{N-[1(S)-ethoxycarbonyl-3-phenylpropyl]-(S)-alanyl}-1,2,3,4-tetrahydroisoquinoline-3(S)-carboxylic acid or the corresponding 1-S-carboxy-compound.

10) Process for the preparation of a compound of formula I as defined in any one of claims 1 to 9, characterized in that the compound is prepared by an appropriate process selected from the following processes a to i:

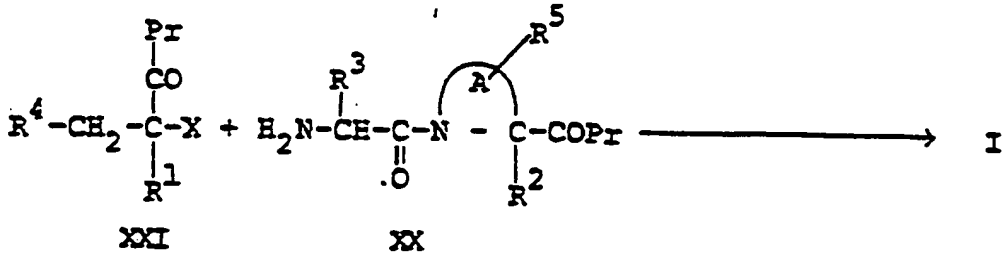
a) for the preparation of a compound of formula I, wherein R^1 is hydrogen: condensation of a ketocompound (XIX) with a depeptide (XX) under reduction



XIX XX I,

wherein A, R^2, R^3, R^4 and R^5 are as define above and Pr stands for a free or a protected hydroxy group;

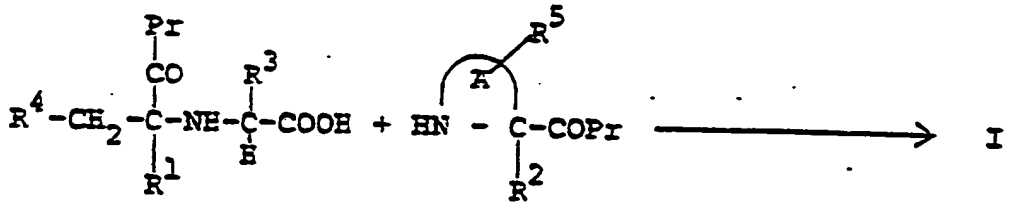
b) alkylation of a dipeptide (XX) by means of a compound of formula (XXI) under basic conditions



XXI XX I

wherein X is chloro, bromo, iodo, alkanesulfonyloxy or arenesulfonyloxy, A, R^1, R^2, R^3, R^4, R^5 are as defined above for compounds of formula I and Pr stands for a free or protected hydroxy group;

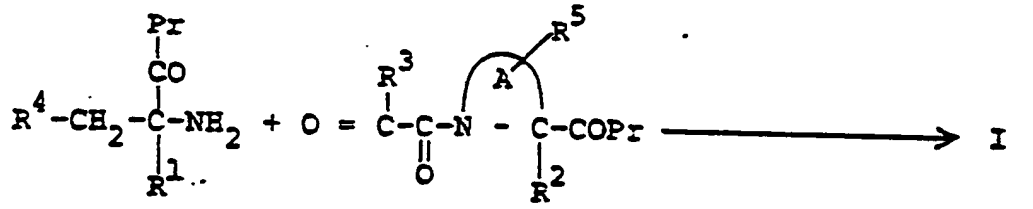
c) condensation of an aminoacid (XXII) with an aminoacid (XXIII) in the presence of a condensing agent



XXII XXIII I

wherein A, R^1, R^2, R^3, R^4, R^5 are as defined above for compounds of formula I, and Pr stands for a free or protected (e.g. by esterification) hydroxy group;

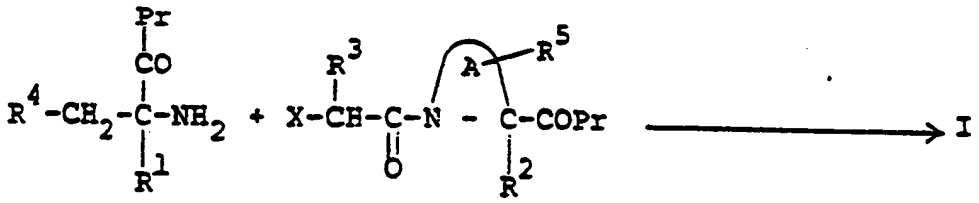
d) condesation of an amino compound (XXIV) with a keto-compound (XXV)



XXIV XXV I

under th conditions described for proc ss a wherein A, R^1, R^2, R^3, R^4, R^5 are as defined above for compounds of formula I and Pr stands for a free or protected (e.g. by esterification) hydroxy group;

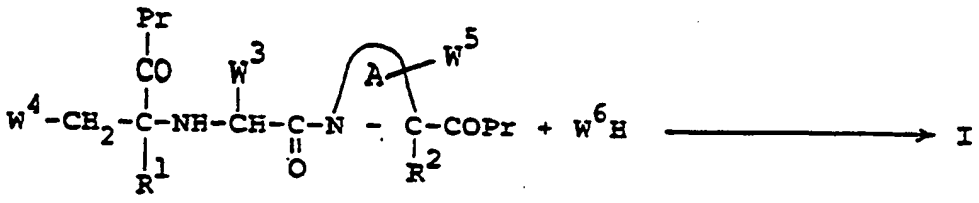
e) alkylation of an amino compound (XXIV) by means of a compound (XXVI)



XXIV XXVI

wherein X is chloro, bromo, iodo, alkanesulfonyloxy or arenesulfonyloxy, A, R^1, R^2, R^3, R^4, R^5 are as defined above for compounds of formula I and Pr stands for a free or protected (e.g. by esterification) hydroxy group, under the conditions described for process b;

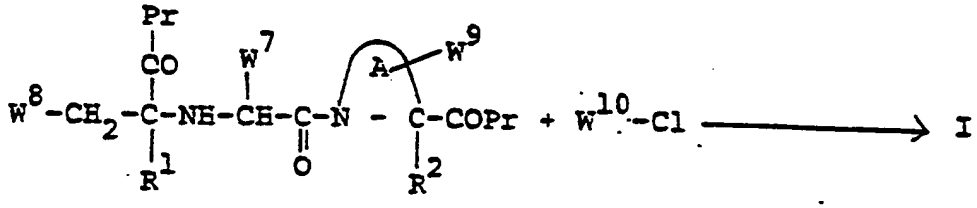
f) for the preparation of a compound of formula I, wherein one of R^3, R^4 and R^5 is a group $Z-(CH_2)_{0-6}-$, wherein Z is Z^5, Z^6, Z^7 Z^8, Z^9 or Z^{10}, preferably Z^7, Z^8 or Z^9: condensation of a peptide of the general formula (XXX) with a compound containing the desired group (XXXI)



XXX XXXI

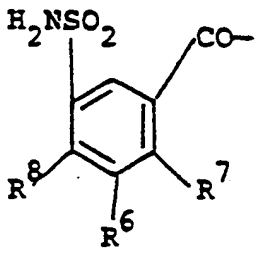
wherein R^1, R^2 and A are as defin d for formula I, Pr is a protected hydroxy group W^3, W^4 and W^5 are defined lik R^3, R^4 and R^5 respectively with the difference that on of W^3, W^4 and W^5 contains an NH_2-group instead of the respective Z^5 to Z^{10}-group; and W^6 is Z^5, Z^6, Z^7, Z^8, Z^9 or Z^{10};

g) for the preparation of a compound of formula I, wherein one of R^3, R^4 and R^5 is a group $Z-(CH_2)_{0-6}-$, wherein Z is Z^1, Z^2 or Z^3: condensation of a peptide f formula XXXII with an appropreately substituted compound of formula XXXIII

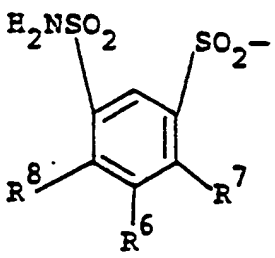


XXXII XXXIII

wherein R^1, R^2 and A are as defined for formula I, Pr is a protected hydroxy group, W^7, W^8 and W^9 are defined lik R^3, R^4 and R^5 respectively, with the difference that on of W^7, W^8 and W^9 contains an NH_2-group instead of the respective Z^1, Z^2 or Z^3 group, and W^{10} is

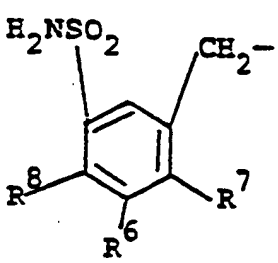


XXXIV



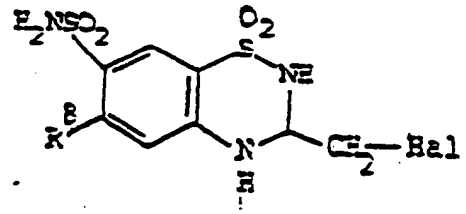
XXXV

or



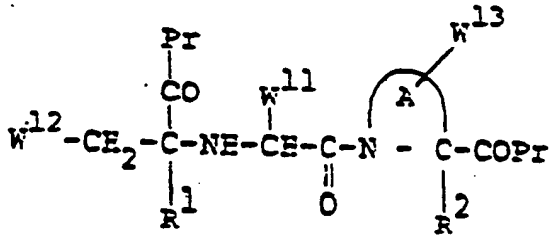
XXXVI

h) for the preparation of a compound of formula I, wherein one of R^3, R^4 and R^5 is a group $Z-(CH_2)_{0-6}-$, wherein Z is Z^4: condensation of a peptide of formula (XXXVII) with a 3 halomethylbenzothiadiazine (XXXVIII)



XXXVIII

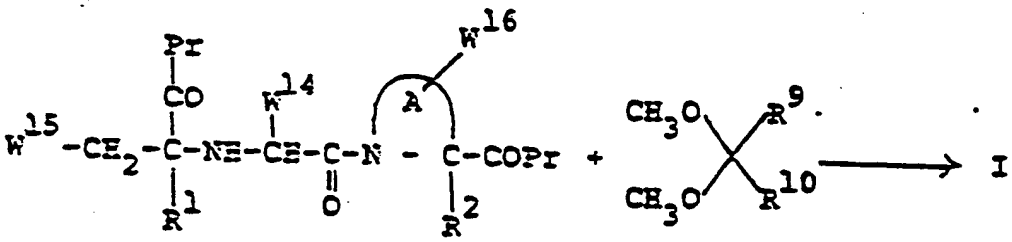
+ ⟶ I



XXXVII

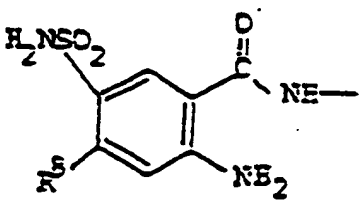
wherein R^1, R^2 and A are as defined for formula I, Pr is a protected hydroxy group, W^{11}, W^{12} and W^{13} are defined like R^3, R^4 and R^5 respectively with the difference that one of W^{11}, W^{12} and W^{13} contains a -SH-group instead of the respective Z^4-group, and Hal is halogen, preferably chloro;

i) for the preparation ofa compound of formula I, wherein one cf R^3, R^4 and R^5 is a gr up $Z-(CH_2)_{0-6}-$, wherein Z is Z^5 or Z^6: condensation of a peptide of formula XXXIX with a compound of formula XXXX

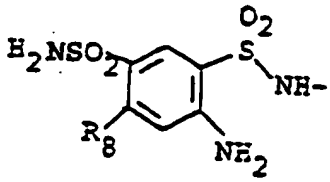


XXXIX XXXX

wherein R^1, R^2, R^9, R^{10} and A are as defined for formula I, Pr is a protected hydroxy group, W^{14}, W^{15} and W^{16} are d - fined like R^3, R^4 and R^5 respectively with the difference that one of W^{14}, W^{15} and W^{16} contains the group



or



respect- ively

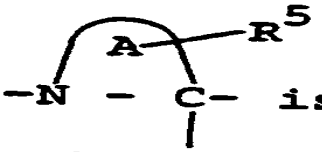
XXXXI XXXXI a

instead of the group Z^5 or Z^6 respectively;

followed by removal of the protecting groups, if necessary, to yield the desired product, and if desired, converting a so obtain d compound of formula I into its ester and/or setting fr e the compound of formula I from its ester r pr paring a salt th reof and, if d sir d, isolating tn pr ferred isomer.

11) A pharmaceutical composition comprising a compound of the general formula I or pharmaceutically acceptable salt or ester thereof as defined in any one of claims 1 to 9 or obtained according to a process of claim 10.

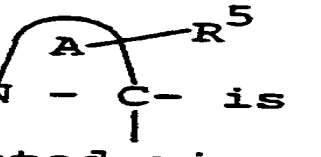
and wherein preferably



is the group of saturated ring) or VIII

3) Process according to that a compound is prepared hydrogen, and/or when Z is hydrogen and R^7 is hydrogen is of the formula XIII or hydrogen or methyl, and/or moiety Z is chloro, and/or

4) Process according to that a compound is prepared hydrogen, the group



is the group of rated ring and R^5 is hydrogen $Z^2-(CH_2)_3-$, wherein R^6 is hydroxy, and R^8 is chloro being

1-{N-[1(S)- thoxycarony
benzenesulfonamidopenty
octahydro-1H-indole-2(S)

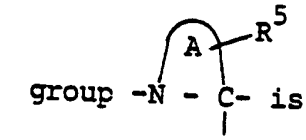
1-{N-[1(S)-ethoxycarbony
benzamidopentyl]-(S)-1a
indole-2(S)-carboxylic a

1-{N-[1(S)-ethoxycarbony
5-sulfamoyl)-benzamidope
octahydro-1H-indole-2(S)

1-{N-[1 (S)-CARBOXY-5-[[(
PHENYL) CARBONYL]AMINO]PE
OCTAHYDRO-1H-INDOLE-2(S)-
1-{N-[1(S)-CARBOXY-5-[[(4
PHENYL] CARBONYL]AMINO]PE
OCTAHYDRO-1H-INDOLE-2(S)-
1-{N-[1(S)-CARBOXY-5-[[(4
CARBONYL]AMINO]PENTYL]-(S
1H-INDOLE-2(S)-CARBOXYLIC

in the free form or in the
in the form of its mono-or

5) Process according to c
compound is prepared, wher
as defined in claim 1, pre
$Z^3-(CH_2)_4-$, Z^4-CH_2-, $Z^5-(C$
$Z^8-(CH_2)_4-$, $Z^9-(CH_2)_4-$ or



group -N - C- is pr

(wherein B is a sat

6) Process accordi

compound is prepare

and/or Z is of the

and R^7 is hydrogen

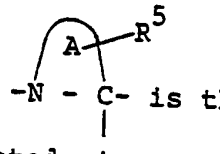
formula XIII or XIV

or methyl, and/or R^8

chloro, and/or R^4 is

7) Process accordin

compound is prepared



group -N - C- is the

saturated ring and R^5

Z^2-$(CH_2)_4$-, wherein R

chloro, and R^4 is ben

1-{Nα-[1(S)-ethoxyca

3-sulfamoyl)benzenes

octahydro-1H-indole-

1-{Nα-[1(S)-ethoxycar

[(4-chloro-3-sulfamoy

octahydro-1H-indol -2

[redacted]

l(S)-

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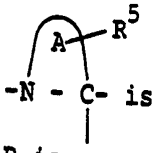
8) Process accor

compound is pr pa

as defined in cla

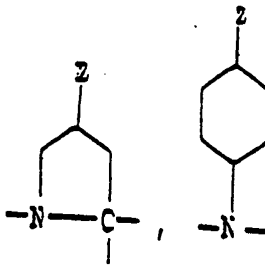
Z^8, Z^9 or Z^{10}; whe



-N - C- is prefera

B is an aromatic r

ring), pref rably



9) Process accordi

compound is prepare

and/or when Z is of

and R^7 is hydrogen

formula XIII or XIV

or methyl, and/or R

chloro, and/or R^3 i

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ASSIFICATION OF THE
PLICATION (Int. Cl. ³)

07 C 103/52
61 K 37/02

CHNICAL FIELDS
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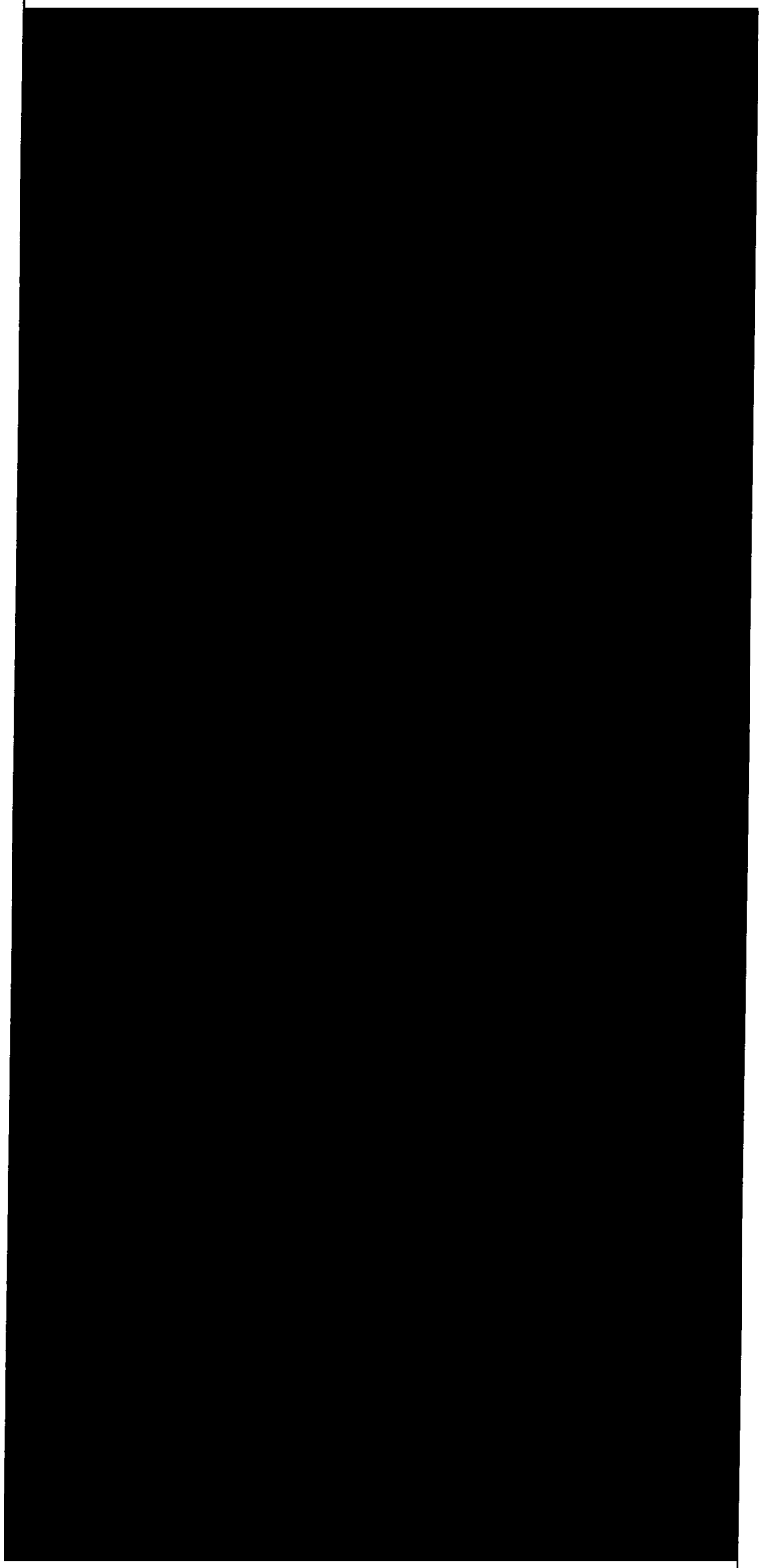

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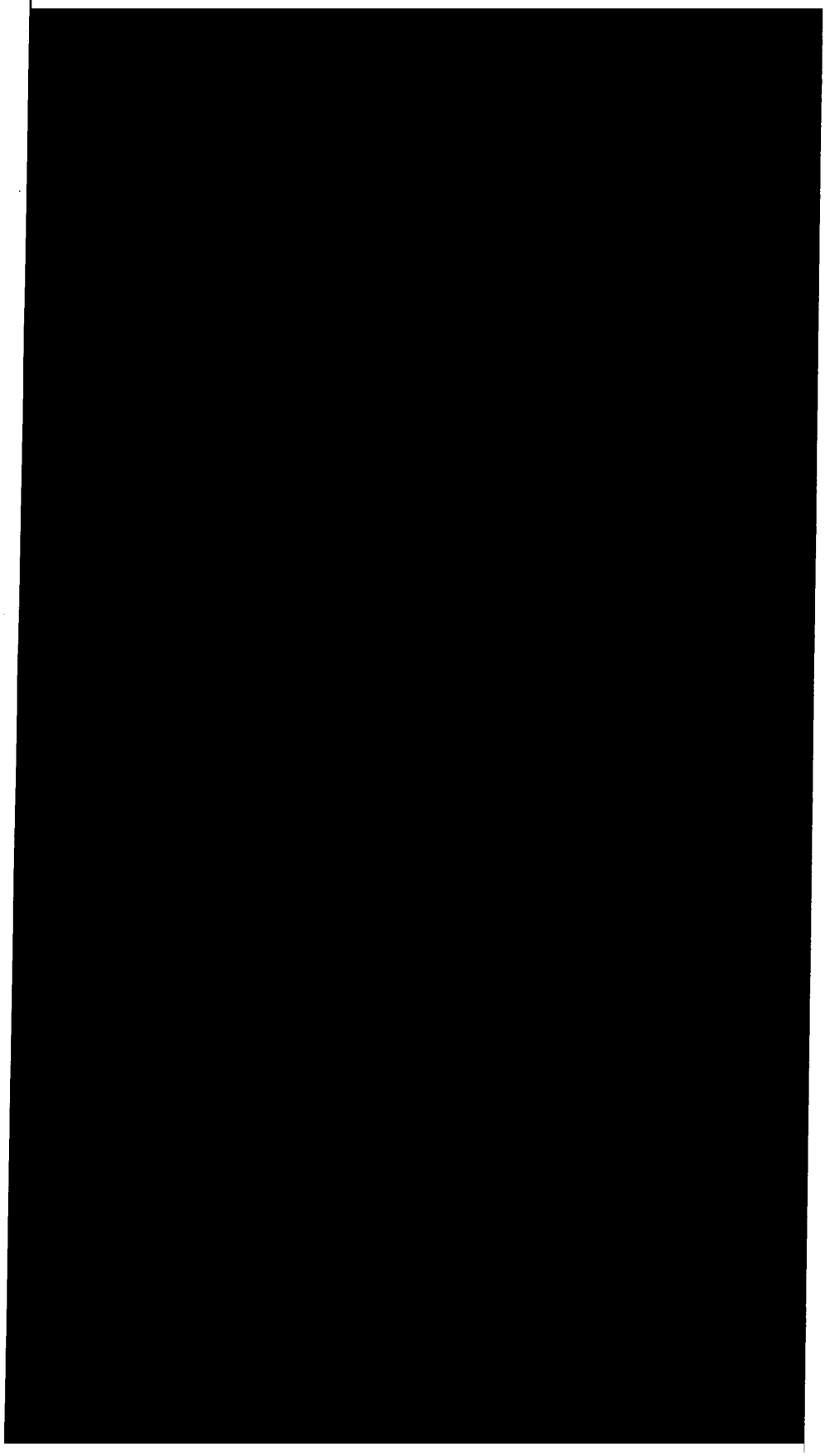

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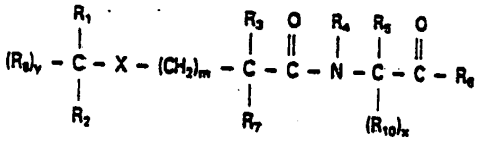
(54) Novel complex amido and imido derivatives of carboxyalkyl peptides and thioethers and ethers of peptides.

(57) Novel inhibitors of angiotensin converting enzyme are disclosed which have the general formula



wherein R_1 and/or R_3 form complex amides and imides thereof, X = S, O or NR_9, R_4 and R_8 form with –N–C– a 4-6 membered ring structure as described and the other R substituents are selected from a variety of disclosed groups.

Background of the Invention

Angi tensin c nverting enzyme (peptidyldipeptid hydrolas , h reinaft r referred to as ACE) ccupi s a central role in the physiology of hyp rtension. The nzym is apable of converting the decapeptide angiotensin I, having the sequence

AspArgValTyrIleHisProPheHisLeu

to an octapeptide, angiotensin II, by removal of the carboxy-terminal HisLeu. The symbols for the foregoing ch mical moieties and others used throughout this application are explained in the following table:

Arg = arginine
Asp = aspartic acid
Boc = t-butyloxycarbonyl
Cbo = carbobenzyloxy
>Glu = pyro-L-glutamic acid
Gly = glycine
Hip = Hippuric acid (Benzoyl-glycine)
His = histidine
Ile = isoleucine
Leu = leucine
Phe = phenylalanine
Pro = proline
ΔPro = 3,4-dehydroproline
Ser = serine
Tos = tosyl
Trp = tryptophan
Tyr = tyrosine
Val = valine
Pht = phthaloyl
ACE = angiotensin converting enzyme
Hepes = N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid

In each instance the symbol for any amino acid is also used herein at times to refer to a mono-or-di-valent radical of such acid and those of ordinary skill in the art will readily understand the context of each specific use.

Angiotensin I is formed by the action of the enzyme renin, an endopeptidase found in kidney, other tissues and plasma, on a serum α-2 globulin.

Blood pressure is affected by certain peptides found in the blood. One of these, angiotensin II, is a powerful pressor (blood pressure elevating) agent. Another, bradykinin, a nonapeptide with the sequence ArgProProGlyPheSerProPheArg is a powerful depressor (blood pressure lowering) agent. In addition to a direct pressor effect, angiotensin II stimulates release of aldosterone which tends to elevate blood pressure by causing retention of extracellular salt and fluids. Angiotensin II is found in measurable amount in the blood of normal humans. However, it is found at elevated concentrations in the blood of patients with renal hypertension.

The level of ACE activity is ordinarily in excess, in both normal and hypertensive humans, of the amount needed to maintain observed levels of angiotensin II. However, it has been found that significant blood pressure lowering is achieved in hypertensive patients by treatment with ACE inhibitors. [Gavras, I. et al., New Engl. J. Med. 291, 817 (1974)].

ACE is a peptidyldipeptide hydrolase. It catalyzes the hydrolysis of the penultimate peptide bond at the C-terminal end of a variety of acylated tripeptides and larger polypeptides having an unblocked α-carboxyl group. The action of ACE results in hydrolytic cleavage of the penultimate peptide bond from the carboxyl-terminal end yielding as reaction products a dipeptide and a remnant.

The reactivity of the enzyme varies markedly depending on the substrate. At least one type of peptide bond, having the nitrogen supplied by proline, is not hydrolyzed at all. The apparent Michaelis constant (Km) varies from substrate to substrate over several orders of magnitude. For general discussion of the kinetic parameters of enzyme catalyzed reactions, see Lehninger, A., Biochemistry, 2nd. Ed., Worth Publishers, Inc., New York, 1975, pp. 189-195. Many peptides which are called inhibitors of the enzymatic conversion

ngiotensin I t angiotensin II are in fact substrat s
ng a lower Km than angiotensin I. Such peptides ar more
erly termed competitive substrates. Exampl s of comp t-
e substrates include bradykinin, and the peptide BPP_{5a}
o called SQ20475) from snake venom, whose sequence
luLysTrpAlaPro.

Num r us synthetic peptide derivatives have been shown
e ACE inhibitors by Ondetti, et al. in U.S. patent
2,337 issued August 27, 1974.

Th role of ACE in the pathogenesis of hypertension
prompted a search for inhibitors of the enzyme that
d act as antihypertensive drugs. See for example U.S.
nts 3,891,616, 3,947,575, 4,052,511 and 4,053,651. A
ly eff ctive inhibitor, with high biological activity
orally administered, is D-3-mercapto-2-methylpropanoyl-
olin , designated SQ14225, or "captopril" disclosed in
patent 4,046,889 to Ondetti et al., issued September
977, and in scientific articles by Cushman, D.W. et al.,
hemistry 16, 5484 (1977), and by Ondetti, M. et al.,
nce 196, 441 (1977). The inhibitor SQ14225 reportedly
an I_{50} value of 2.3×10^{-8}M. The I_{50} value reported by
man, et al., supra is the concentration of inhibitor
ired to produce 50% inhibition of the enzyme under a
dard assay system containing substrate at a level sub-
ntially above K_m. It will be understood that I_{50} values
directly comparable when all potential factors affecting
r action are kept constant. These factors include the
rce of enzyme, its purity, the substrate used and its
centration, and the composition of the assay buffer. All
data reported herein have been performed with the same
ay system and same enzyme (human urinary ACE) and with
same l vel of substrate and are therefore internally
sistent.

The mode of action of SQ14225 has been based upon a
el of the active site of ACE dev loped by analogy with
better known related enzym , carboxypeptidase A. The
ive site was postulated to have a cationic sit for
ding the carboxyl end group of the substrate and a

t or cleft capable f binding th sid chain of th minal amino acid and providing sp cially tight bind- or th h terocyclic ring of a terminal proline ue. A similar pock t for the p nultimat amin acid ue was postulated, and the published data suggested a r stringent steric requirement, since the D-form of the itor was substantially more potent than its stereo- r r the 3-methyl and unsubstituted analogs. The ydryl group on the inhibitor, postulated to be bound e active site near the catalytic center, was believed ay a central role in inactivation of the enzyme by ning with the zinc moiety known to be essential for ytic activity. Substituents on the sulfhydryl, such as nyl gr up, and a S-acetyl derivative, substantially ed p tency of the inhibitor. See Cushman, D.W., et al., emistry, supra.

In vitro study of the mechanism by which SQ14225 and nalogs act to inhibit ACE has been somewhat hampered by nstability of these molecules under ambient conditions. xample, it has been observed that a fresh aqueous .on of concentration, e.g., 1 mg per ml of SQ14225 at f about 8 becomes substantially less active upon .ng f r as little as 30 minutes, and that activity nues to decrease as the solution stands for longer is. It is believed that this loss in activity is the result of dimerization of SQ14225 occurring at l fhydryl end groups, whereby a disulfide is formed Is largely inactive as an inhibitor. Since the free ydryl group is highly reactive and may be readily .ed to polar acidic moieties such as sulfone and ide groups, it may also be that the observed in vitro f activity of aqueous solutions of SQ14225 on standing some part a consequence of one or more such ion reactions, with formation of a sulfone or sulf- which do s not function effectively as an inhibitor E.

uch reports of SQ14225 clinical testing as are tly availabl , some of which refer to the compound under

ril" or "Capoten", suggest that the product
stable in the normal gastric and intestinal
most patients t b an effective inhibitor
nistered orally. It is not yet clear, how-
ere may be a group of patients for which
antially ineffective. Because of the high
e free sulfhydryl group, SQ14225 could
ed disulfides with serum, cellular proteins,
r free sulhydryl group-containing substances
r int stinal environments, in addition to
for dimer formation or oxidative degradation
xed disulfide with protein may be antigenic
aional allergic reactions have been clinically
avras, et al., New England J. Med. 298, 991
des and oxidative degradation products of
ed, may at best be expected to be largely
nhibitors. It may be postulated accordingly
se to SQ14225 may vary with conditions of
ad among individual patients. Moreoever, in
.ients, unwanted side effects may occur and
effective concentration of the inhibitor
e difficult to control.
cts of SQ14225 in man include fevers and
et al, supra). Hoorntje et al., The Lancet,
'8Q) d scribe the performance of renal
tients treated with SQ14225. All biopsies
f immune complex deposition along the
nt m mbranes, although 9 of 13 patients
at th time of the biopsy. These authors
milarities of their findings with those
r drug with a free mercapto group, D-penicill-

to devise better inhibitors of angiotensin
that are more stable than captopril and
duce D-penicillamin -like adverse effects,
repared a series of compounds having side
nalogous to an effective substrate for the
he-Ala-Pro and disclosed them in copending

Ser. No. 187992 filed Septemb r 17, 1980.
e th class of carboxyalkyldipeptides
l sed in European published application of
published on r about June 25, 1980. Th
ion defines compounds such as N-[L-1-carboxy-
ropyl]D,L-Ala-L-Pro, N-[L-1-carboxy-3-(carbo-
opyl]-D, L-Ala-L-Pro, and analogs i.e.,
s of N-(lower alkylene)Ala-Pro. These two
were found to be unexpectedly effective in
tensin converting enzyme in vitro, that is
low I_{50}, in the order of 10^{-9}M. In contrast
relat d analog of the two named compounds, i.e.,
-(carbopyrrolide)ethyl]-D,L-Ala-Pro, was
much higher I_{50}, in the order of 10^{-7}M, a
itor likely to be too low for anti-hyper-
eness. It is believed, therefore, that
s of N-(lower alkylene)-Ala-Pro and related
npredictable effects on angiotensin converting

, the removal of iodine from N-[L-1-carboxy-3-
lide)propyl]-D,L-Ala-L-Pro increases intra-
ness three-fold, an unexpectedly large
e in vivo effect of the anti-hypertensive
s invention. Hence, amides and imides of
e)-D,L-Ala-Pro and related compounds are new
rising effectiveness in lowering blood

since the compounds of this invention do not
fhydryl group of SQ14225, they are most
ble and have durations of action much longer
225. Thus, inhibitors of this invention
treating hypertension with less frequent
than required for SQ14225 and may be capable
n und r less rigorously controlled conditions.
n of the invention

itors of ACE are disclosed which base the

or alk xybenzyl in which the alkoxy
phenoxyphenyl, phenoxybenzyl,
oxyphenyl or a thio ther anal g of

CH_3 wherein n = 0-4 and B = H

roup, or an -SB analog thereof;
$(CH_2)_p$ COSZ wherein p = 0 - 3 and
1 - 5 carbon alkyl group, or an
y acceptable salt;

CH_3 or $-(CH_2)_n - \underset{\underset{\underset{O}{\|}}{C - Z}}{\overset{|}{CH}} - CH_3$

C - Z
O

$-(CH_2)_n - \underset{\underset{\underset{O}{\|}}{C - SZ}}{\overset{|}{CH}} - CH_3$

to 4 and Z each have the same

$\overset{D}{\underset{|}{CH}}$

H - or HS - $(CH_2)_n$ - CH -
h ayl, thienyl or a 1 - 3 carbon

$C(CH_3)_2$ -, HS - $(CH_2)_n$ - $C(CH_3)_2$ -,
$C(CH_3)_2$ - or -p-mercaptophenyl-
n n has the same significance as

henyl - $(CH_2)_n$ - CH_2 - or p-hydroxy-
herein the phenyl ring has one or
tuents and n has the same signifi-

$\overset{OH}{\underset{|}{CH}}$ - or CH_3 $\overset{SH}{\underset{|}{(CH_2)_n - CH}}$ - wherein
ce as above;

or NO_2 - alkylene containing one
tuent and having 1 - 6 carbon

rcapto-phen xyb nzyl;

$(CH_2)_n$ -, $ZS-(CH_2)_q - \overset{O}{\overset{\|}{C}} - (CH_2)_n$ -,

$NO_2(CH_2)_q - \overset{O}{\overset{\|}{C}} - (CH_2)_n$ -,

-, $NH_2NH - (CH_2)_q - \overset{O}{\overset{\|}{C}} - (CH_2)_n$ -,

, $ZA - \overset{O}{\overset{\|}{C}} - (CH_2)_q - \overset{O}{\overset{\|}{C}} - (CH_2)_n$ -

$CH_2)_n$ - wb r in q = 1 - 5 and n
ne same significance as above;

$\overset{OH}{\overset{|}{C}}H - (CH_2)_n$ -,

$NH_2-(CH_2)_q - \overset{O}{\overset{\|}{C}}H - (CH_2)_n$ -,

-,

$- (CH_2)_n$ -,

$ZS - (CH_2)_q - \overset{OH}{\overset{|}{C}}H - (CH_2)_n$ -,

-, or

n,
same significance as above;

$- \overset{O}{\overset{\|}{C}} - (CH_2)_n$ -, G - NH $(CH_2)_q$ -

$\overset{O}{\overset{\|}{C}} - (CH_2)_n$ -,

ese structures may b

, -O  , OCH_2  ,

SH, $-SCH_3$, -S  ,

, $-CH_2OH$, propyl,
anidino and that any of
lisubstituted with -OH,
on of two of this group

y be H, an alkyl group
ter m i ty hydrolyzable
t -OH, or an ionically
cceptable nontoxic salt;
droxymethyl, aminomethyl

nyl, hydroxymethyl,
ethyl, mercaptomethyl,
thoxycarbonylmethyl,
CH_2=CH-CH_2-, isobutyl,
ydroxyalkyl of 2-3
mido, acetamido,
lkyl ne group has 1-4
kylene wherein the
isoalkyl ne group
, alkanoylamine of 1 - 5
, ph nylamin , alkyl-

e general formula

ranched chain alkyl of
cylcycloalkylalkylene,

oups may be
ngth;
anched chain
ted alkyl
en ,
sub tituted
ne substituent
ay b
, and are
$_2$, carboxy,
aminom thyl,
yl, meth xy-
cyanomethyl,
ercaptoalkyl
at ms,
amin alkylene
-alkoxy-
tains 1-5
rbons,
lamide of
ons, lower
amin , acyl-
, lower
r alkoxy;
of 1-6

rein the
1-6 carbons;
th alkoxy
zyl, benzyl-
og of any f

and B=H

[redacted]

it bei

monosu

Cl, Br

-SCH$_2$
guanid
th 5-
F, Cl,
of sub
R
of 1-3
und r
b nd d
R
or merc
R
amin me
methoxy
yanome
m rcapt
carbon
phthalo
carb n
alkyl g
contain
carb ns
amine o
and

A.

wherein
(i)
1-6 carb
or alky

(ii) are
carbons or alk
(iii) phe
(iv) alk
the same or di
(v) sub
alkyl, substit
cycloalkylalky
substituted al
phenyl or subs
or substituent
included in an
selected from
$CONH_2$, lower a
dihalomethyl,
methyl, methyl
benzyl, acetox
of 2-3 carbon
acetylthio thy
wherein the al
carbonyl isoal
carbons and th
benzoylamino,
1-5 carbons, pl
alkoxy, arylox
amino, arylami
alkylthio, aryl
(vi) alkyl
carbons, alkylt
(vii) alkyl
alkyl groups ma
(viii) alkox
group has 1-3
oxybenzyl or be
them;
(ix) $-(CH_2$